The Comparative Antiarrhythmic Actions of Lidocaine and its Quaternary Derivative, Methyl Lidocaine

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SUMMARY

Lidocaine has proved to be an effective antiarrhythmic agent in the management of ventricular arrhythmias subsequent to acute myocardial infarction. Lidocaine's short duration of action and its propensity for producing central nervous system (CNS) stimulation suggest that a safer and more effective therapeutic agent, based on a modification of the lidocaine structure, might be found. The quaternary ammonium compound, methyl lidocaine, was synthesized and its actions in experimentally-induced arrhythmias were studied and compared to those of lidocaine. The antiarrhythmic effects of lidocaine and methyl lidocaine were examined in the anesthetized dog against ouabain-induced ventricular tachycardia and in conscious animals with ventricular tachycardia 48 hours after two-stage ligation of the anterior descending coronary artery. Both pharmacological agents were capable of reversing digitalis-induced arrhythmias and restoring normal sinus rhythm in animals 48 hours after surgical ligation of the anterior descending coronary artery, but methyl lidocaine remained effective for a significantly longer period and its continual administration was not associated with signs of CNS toxicity. In experiments designed to determine the electrical fibrillation threshold, both drugs were able to reduce the vulnerability to ventricular fibrillation but the time course of action for each drug differed. Lidocaine had an immediate effect of increasing the ventricular fibrillation threshold whereas the peak effect of methyl lidocaine was delayed and the increase in the fibrillation threshold lasted longer. This study concludes that the quaternary derivative of lidocaine, methyl lidocaine, possesses antiarrhythmic properties similar to those of lidocaine, but differs in its duration of action and lack of overt stimulatory effects upon the central nervous system.

Additional Indexing Words:
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Automaticity
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Fibrillation threshold
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MOST SUDDEN CARDIAC DEATHS due to atherosclerotic heart disease can be attributed to ventricular fibrillation. The antiarrhythmic effect of lidocaine was noted by Southworth et al. in 1950, and in more recent years, lidocaine has been used extensively in the coronary care unit and in this setting has been associated with the decreased mortality. In addition, its relative lack of cardiac depressant effect at therapeutically effective plasma concentrations and its rapid onset of action have made lidocaine the agent of choice in the treatment of ventricular arrhythmias. Unfortunately, lidocaine is rapidly metabolized and thus must be administered as a continuous intravenous infusion in order to maintain therapeutically effective plasma concentrations. In addition, infusion rates above 50 μg/kg/min, or the presence of hepatic dysfunction, or congestive heart failure, may lead to plasma levels in excess of 7 μg/ml, which are associated with central nervous system (CNS) toxicity.

Since the quaternary form of a compound is highly charged at all body pH values and has a limited ability to enter the central nervous system, it was considered important to examine the antiarrhythmic effectiveness of methyl lidocaine, the quaternary derivative of lidocaine. It has been demonstrated recently that the quaternary derivative of propranolol, dimethylpropranolol, possesses marked antiarrhythmic effects in experimentally-
induced arrhythmias, suggesting that the quaternary form of other antiarrhythmic agents such as lidocaine would be similar to or more effective than the parent compound. The present study has provided evidence that the quaternary derivative of lidocaine, methyl lidocaine, is effective against experimentally induced arrhythmias and possesses definite advantages over lidocaine with respect to its duration of action and its lack of central nervous system toxicity.

**Methods**

**Ouabain-Induced Arrhythmias in the Anesthetized Dog**

Male mongrel dogs between 9.2 and 12.0 kg were anesthetized with intravenous pentobarbital sodium, 30 mg/kg. The femoral artery was cannulated and blood pressure was measured via a Statham transducer. The right vagus nerve was sectioned in the cervical region and its distal end was stimulated periodically with 1.0 msec square wave stimuli at a frequency of 40 cycles per second at 6.0 to 8.0 V. Ventricular tachycardia was induced by the intravenous administration of ouabain 40 μg/kg initially, 20 μg/kg after 30 min, and an additional 10 μg/kg every 15 minutes thereafter until ventricular tachycardia developed.

The criteria used to determine antiarrhythmic activity were 1) reversion to normal sinus rhythm for a period of not less than 30 minutes, and 2) the failure of right vagal stimulation to expose automatic ventricular foci during the period of vagal-induced sinoatrial arrest or slowing.

**Ventricular Arrhythmias after Coronary Artery Ligation**

Mongrel dogs of both sexes and 12 to 15 kg in weight were anesthetized with intravenous pentobarbital sodium, 30 mg/kg. Mechanical ventilation with room air was instituted through a cuffed endotracheal tube by means of a Harvard respirator. Under aseptic conditions, the heart was exposed through the fifth left intercostal space. The anterior descending branch of the left coronary artery was dissected free about 5 to 8 mm distal to the edge of the left atrial appendage. A double ligature was passed under the artery and the vessel was occluded in two stages according to the method described by Harris. Sterile catheters (0.040 in I D) were placed in the external jugular vein and the left carotid artery. The catheters were exteriorized via a small stab wound at the back of the neck and were maintained patent by periodic flushing with sterile heparin solution.

The animals were studied 48 hr later in the unanesthetized state. The lead II electrocardiogram and arterial blood pressure were continuously recorded while the animals were supported in a harness and maintained in a quiet environment. At the time of study, all animals displayed spontaneous ventricular arrhythmias which were characterized by multifocal ventricular tachycardia. All drugs to be studied were administered via the jugular vein catheter.

**Determinations of the Ventricular Fibrillation Threshold**

The experiments were performed on mongrel dogs of both sexes, 12 to 16 kg in weight, anesthetized with pentobarbital sodium (30 mg/kg). The animals were maintained by positive pressure ventilation at a minute volume determined from a body weight nomogram. The hearts were exposed through a thoracotomy in the fifth intercostal space and suspended in a pericardial cradle. Lead II of the electrocardiogram was monitored continuously on a Tektronix oscilloscope.

Double bipolar silver-silver chloride electrodes (1 mm in diameter), embedded in an acrylic plaque, were sutured to the surface of right ventricle. One pair of electrodes delivered the basic pacing stimulus while the second pair of electrodes delivered a gated train of impulses during the vulnerable period of the T wave of the electrocardiogram. The sinoatrial node was crushed and the ventricular rate maintained electrically at a frequency of 2 cycles per second. The fibrillation pulses, 60 Hz frequency and 2 msec duration, were synchronized to the ventricular pacing stimulus and were delivered immediately after the QRS complex of every sixth basic driven beat, and lasted 350 msec, thus scanning the T wave and the vulnerable period of the heart. There were 20-21 of these pulses in the train. The current delivered was measured directly by recording the voltage drop across a precision one kohm resistor in series with the electrodes. The current intensity was increased in increments of 0.5 milliamperes (ma) until ventricular fibrillation developed. The ventricular fibrillation threshold was defined as the minimum current in milliamperes which induced ventricular fibrillation. When fibrillation occurred, the heart was immediately defibrillated using a capacitor discharge DC defibrillator. The heart was allowed to recover for 8-30 min after each determination.

All data were compared by the method of self-paired analysis. All values are expressed as mean ± the standard error of the mean.

Methyl lidocaine used was the methane sulfonate salt; lidocaine as the HCl salt. All dosages are expressed in terms of the base compound.

**Results**

**Effects of Lidocaine and Methyl Lidocaine upon Ouabain-Induced Ventricular Tachycardia**

Ventricular tachycardia resulted in each of ten dogs after the administration of ouabain in an average dose of 60 μg/kg. Once the ventricular rhythm had been established for at least 30 min, the distal end of the right vagus nerve was stimulated to demonstrate the ventricular origin of the ectopic pacemaker. Vagal stimulation did not influence the rate of the ventricular focus, a finding which suggested that the ectopic pacemaker was located below the A-V junction. Thus, the rhythm disturbance could be due to a digitalis-induced enhanced automaticity or intraventricular re-entry.

The animals were treated with either lidocaine or
methyl lidocaine, with five animals assigned to each treatment group. Lidocaine was administered as an intravenous bolus injection of 2 mg/kg every 3 min until normal sinus rhythm was restored, while methyl lidocaine was infused intravenously at a constant rate of 5 mg/min, an average rate of 1.6 mg/kg every 3 min for the five animals, until normal sinus rhythm was restored. The average dose of lidocaine required to restore normal sinus rhythm was 4.0 mg/kg (range 2–10 mg/kg) whereas the average effective dose of methyl lidocaine was 4.4 mg/kg (range 3.6–10.0 mg/kg). The primary difference between the action of the two drugs was with respect to their duration of action. Reversal with lidocaine was transient in all five animals, with a mean time to return of the arrhythmia of 9.2 min. In contrast, the reversal induced by methyl lidocaine was maintained for at least 60 min. At this point, each of the animals in the latter group received 80 units of regular insulin (I.V.) for the purpose of decreasing serum potassium. In spite of this intervention none of the five methyl lidocaine-treated animals had a recurrence of ventricular ectopic rhythms. Figures 1 and 2 are representative experiments showing the effects of lidocaine and methyl lidocaine, respectively, on ouabain-induced ventricular tachycardia.

Effects of Lidocaine and Methyl Lidocaine after Coronary Artery Occlusion

The anterior descending coronary artery was ligated in each of six dogs. Each animal was then studied in the unanesthetized state 48 hr postligation while resting quietly in a harness. Lidocaine

![Figure 1](https://circuitdbjournals.org/)

**Figure 1**

The effect of lidocaine upon a ouabain-induced ventricular arrhythmia in the dog. Lower portion of each panel shows the systemic arterial blood pressure. The upper portion of each tracing shows the lead II electrocardiogram. Paper speed equals 25 mm/sec. The onset of vagal stimulation is indicated by the arrow and is continued for 10 sec. Left upper panel: control record showing effects of stimulation of the distal end of the cut right vagus nerve. The parameters of vagal stimulation were those sufficient to produce a sinus slowing. Right upper panel: ventricular arrhythmia resulting from ouabain. Stimulation of the right vagus nerve does not affect the ventricular ectopic rhythm. Left lower panel: tracing obtained after restoration of normal sinus rhythm by the intravenous administration of lidocaine. Stimulation of the right vagus nerve once again leads to ventricular standstill indicating that lidocaine has effectively suppressed the ouabain-induced ectopic focus. Right lower panel: within 10 minutes after the administration of lidocaine, the ventricular arrhythmia has returned and is not influenced by stimulation of the right vagus nerve. Thus, suppression of the ventricular ectopic focus by lidocaine was limited to a period less than 10 min.
LIDOCAINE AND METHYL LIDOCAINE

Figure 2

The effect of methyl lidocaine upon a ouabain-induced ventricular arrhythmia. The experimental design is similar to that shown in the previous figure although lead II is shown in the bottom trace of each panel. Note that methyl lidocaine suppressed the automatic ventricular focus and its antiarrhythmic effect was still apparent 60 min after its administration, as evidenced by the fact that vagal stimulation and sinoatrial arrest did not demonstrate the presence of enhanced ventricular automaticity.

was administered to three of the animals via the jugular vein as a bolus injection of 1 mg/kg every 5 min until conversion or until signs of acute toxicity developed. The remaining three animals received methyl lidocaine in a dose of 5 mg/kg injected over the course of 5 min.

In the three animals receiving lidocaine, multifocal ventricular tachycardia was the predominant rhythm with 88.9% (91 ± 20.3 out of 132 ± 16.7 SEM) of the beats being of ventricular origin. Each lidocaine injection caused a transient decrease in the ventricular ectopic rate. However, this effect had disappeared by the end of the five-minute drug administration cycle. As drug administration was continued, signs of central nervous system stimulation became apparent. Clonic convulsions appeared after the fourth, sixth, and ninth doses, respectively, in the three animals, and this precluded further lidocaine administration. Thus, with repeated doses, the signs of central nervous system (CNS) toxicity became more marked, whereas, the antiarrhythmic activity of lidocaine was never more extensive nor prolonged than that seen after the first dose of 1 mg/kg.

The three animals in the methyl lidocaine-treated group had a similar rhythm disturbance in which 87.4% (111 ± 11.9 out of 127 ± 6.4 SEM) of the total number of heart beats was of ventricular origin. Methyl lidocaine, 5 mg/kg, significantly reduced the number of ventricular ectopic beats and the rhythm in each of the three dogs was predominantly of sinoatrial origin and maintained in excess of 3 hours. Figure 3 summarizes the results obtained in the dogs treated with methyl lidocaine. In no instance was there any evidence of central nervous system toxicity due to methyl lidocaine. The effect of methyl lidocaine upon the ventricular arrhythmia due to coronary artery ligation in one of the three dogs is shown in figure 4.

Effects of Lidocaine and Methyl Lidocaine on the Ventricular Fibrillation Threshold

Figure 5 summarizes the results from five control animals in which the electrical threshold for ventricular fibrillation was determined six consecutive times over the course of 120 minutes. As can be seen from the graphic representation of the results, there is little variation in the current intensity of the trains of stimuli needed to produce ventricular
The effect of methyl lidocaine, 5 mg/kg, in three dogs 48 hr after experimentally-induced myocardial infarction. Each animal was studied in the unanesthetized state during the phase of spontaneous ventricular tachycardia and received an intravenous injection of methyl lidocaine. The time in minutes after methyl lidocaine administration is expressed on the abscissa. The heart rate is expressed on the ordinate as beats per minute. The dotted line represents the intrinsic heart rate, that is, the total of all sinus as well as ectopic beats occurring each minute. The solid line represents the ectopic rate, that is, the number of beats occurring each minute which were not of sinoatrial origin. Each point on the graph is the mean of the determinations made in the three animals ± the SEM. Methyl lidocaine produced a significant decrease in the frequency of ventricular ectopic discharge as shown by the solid line. This predominantly normal sinus rhythm produced by methyl lidocaine was maintained in excess of 180 minutes.

fibrillation, even after repetitive determinations over the course of 2 hr. These results demonstrate the reproducibility of the measurement and indicate that previous episodes of fibrillation and defibrillation do not alter the threshold values, thus making it possible to assess the effects of antiarrhythmic agents upon the fibrillation threshold with each animal serving as its own control.

In each of five animals studied, the ventricular fibrillation threshold was increased after the administration of lidocaine (3.1 mg/kg) as an intravenous bolus. The mean control fibrillation threshold for the group was 5.6 ma ± 0.2; 2 min after lidocaine the mean fibrillation threshold was 26.3 ma ± 4.5. As shown in figure 6, the ventricular fibrillation threshold increases rapidly after the administration of lidocaine and then diminishes rapidly. The fibrillation threshold returns to control values between 45–60 minutes after drug administration.

The results obtained with methyl lidocaine, 3.1 mg/kg, are somewhat different from those obtained with lidocaine. The increase in the fibrillation threshold after methyl lidocaine was maximal between 120 to 150 min after drug administration. The mean control value was 5.1 ma ± 0.4 whereas the maximal mean value after drug was administered was 24.6 ma ± 6.0. The results are summarized and compared with the data obtained with lidocaine in figure 6. Although both agents increase the ventricular fibrillation threshold, the time course of action for each drug is markedly different. The maximal increase in the fibrillation threshold after lidocaine is attained in 2 min in contrast to the action of methyl lidocaine, which requires at least 1 to 1½ hr for its peak effect.

Discussion

Lidocaine has been used extensively in the management of cardiac arrhythmias subsequent to

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**Figure 3**

The effect of methyl lidocaine, 5 mg/kg, in three dogs 48 hr after experimentally-induced myocardial infarction. Each animal was studied in the unanesthetized state during the phase of spontaneous ventricular tachycardia and received an intravenous injection of methyl lidocaine. The time in minutes after methyl lidocaine administration is expressed on the abscissa. The heart rate is expressed on the ordinate as beats per minute. The dotted line represents the intrinsic heart rate, that is, the total of all sinus as well as ectopic beats occurring each minute. The solid line represents the ectopic rate, that is, the number of beats occurring each minute which were not of sinoatrial origin. Each point on the graph is the mean of the determinations made in the three animals ± the SEM. Methyl lidocaine produced a significant decrease in the frequency of ventricular ectopic discharge as shown by the solid line. This predominantly normal sinus rhythm produced by methyl lidocaine was maintained in excess of 180 minutes.

**Figure 4**

The effect of methyl lidocaine on the spontaneous ventricular tachycardia in the awake dog 48 hours after a two-stage ligation of the anterior descending coronary artery. Each panel shows the lead II electrocardiogram. H.R. = Heart rate; E.R. = Ectopic rate.
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A comparison of the ventricular fibrillation threshold in a group of 5 dogs undergoing repetitive determinations (6 trials) over the course of 120 minutes. These control experiments demonstrate that progressive changes in the ventricular fibrillation threshold do not occur with repetitive trials of fibrillation and defibrillation.

Acute myocardial infarction and has been considered effective in reducing the incidence of fatal ventricular fibrillation, as well as managing digitalis-induced arrhythmias. The major toxic effects associated with the use of lidocaine are on the central nervous system; when plasma concentrations exceed 7 µg/ml, generalized convulsions occur. Higher plasma concentrations may cause respiratory arrest. Secondly, lidocaine quickly diffuses throughout the body tissues after intravenous administration and is rapidly metabolized by hepatic mechanisms. Its relatively short half-life of 30–40 min when administered as a single bolus injection is consistent with the rapid termination of its antiarrhythmic activity as observed in the present study.

Although pharmacokinetic data on methyl lidocaine are not available at present, the derivative apparently differs from lidocaine with respect to its duration of action. Recently it has been reported that the antiarrhythmic activity of the quaternary derivative of propranolol lasts longer than that of its parent compound. Thus, the quaternary ammonium derivative of lidocaine, methyl lidocaine, could differ significantly in the manner in which it is metabolized. It is obvious that one significant difference between lidocaine and methyl lidocaine lies in the manner in which the drugs distribute in the body. The important distribution kinetics of these agents are not necessarily demonstrated by venous blood sampling. Rowland et al have calculated the volume of distribution of lidocaine. They found that the rate of equilibration between plasma and heart and brain was rapid. In fact, central and cardiac effects were noted within seconds after the bolus administration of lidocaine. The cardiac effects (i.e., antiarrhythmic effects) are desired, while the effects on the CNS (e.g., depression leading to stimulation and convulsions) are certainly the most serious complications encountered with the use of lidocaine. It is logical to assume from our data that both lidocaine and methyl lidocaine are capable of distributing to the myocardium and exerting an antiarrhythmic effect. However, it appears that at the therapeutic doses required, only lidocaine reached the central nervous system in high enough concentration to produce

Figure 6

A comparison of the time course of changes in the fibrillation threshold after a single intravenous injection of either lidocaine (N = 5) or methyl lidocaine (N = 5). Each drug was administered in a dose of 3.1 mg/kg calculated as the base. The control fibrillation thresholds are shown at time zero; the mean values for the lidocaine and methyl lidocaine were, 5.6 ma ± 0.2 and 5.1 ma ± 0.4, respectively. After lidocaine the mean fibrillation threshold equaled 26.3 ma ± 4.5. The increase was immediate and declined rapidly. In contrast, methyl lidocaine caused a slow rise in the fibrillation threshold, which averaged 24.6 ma ± 6.0 after 150 minutes.
toxic manifestations, and therefore the quaternary form of lidocaine could eliminate this undesirable aspect without a loss in antiarrhythmic effectiveness. Gillis et al.\textsuperscript{14} have compared the antiarrhythmic actions of lidocaine and methyl lidocaine in the unanesthetized animal and have observed that the latter did not induce convulsions or a significant increase in EEG activity, whereas lidocaine caused tonic-clonic seizures in three of five animals studied. Since both lidocaine and methyl lidocaine possess equal degrees of local anesthetic activity,\textsuperscript{17} the most likely explanation for the failure of methyl lidocaine to produce central nervous system toxicity lies in its failure to cross the blood brain barrier.

It is doubtful that the present results can be attributed to the difference in the means of administration of methyl lidocaine and lidocaine in either this work or in the study reported by Gillis et al.\textsuperscript{14} In this study, lidocaine was administered as an intravenous bolus injection in a clinically acceptable fashion. Bigger\textsuperscript{11} has suggested that lidocaine be administered intravenously at rates of 0.5 to 1 mg/kg every 3 to 5 min to a total dose of 200-300 mg. Gerstenblith et al.\textsuperscript{15} have demonstrated that the administration of an intravenous bolus injection of 2 mg/kg of lidocaine produced a significant increase in the ventricular fibrillation threshold. They also demonstrated that the infusion of 70 μg/kg/min of lidocaine after the initial loading dose was sufficient to maintain this effect. It has been suggested, however, that it is the continued intravenous infusion of lidocaine that can lead to central nervous system toxicity.\textsuperscript{16} It was the purpose of this study to present an alternative to the continued infusion of lidocaine after an initial loading dose. It is true that the delayed onset of methyl lidocaine’s antiarrhythmic action could be considered a drawback. On the other hand, the initial bolus injection of lidocaine followed by intravenous methyl lidocaine could provide a therapeutic regimen which was effective and yet safe from adverse central effects.

In each of the experimentally-induced arrhythmias, methyl lidocaine proved to be at least as effective an antiarrhythmic agent as lidocaine. Both drugs were capable of reversing ouabain-induced ventricular tachycardia by suppressing the digitalis-induced ectopic pacemaker. Similarly both drugs have been demonstrated to be able to reduce or abolish the disturbances in ventricular rhythm which develop secondary to acute occlusion of the anterior descending coronary artery of the dog’s heart. Gillis et al.\textsuperscript{18} further noted that methyl lidocaine and lidocaine were effective in reducing the number of ectopic beats and runs of ventricular tachycardia after acute myocardial ischemia in the canine heart. As in the present study, the previous investigators found a difference in the duration of antiarrhythmic effectiveness.

Spear et al.\textsuperscript{18} have shown that lidocaine increases the ventricular fibrillation threshold in the canine heart and that the time course of the effect is related to the time course of the blood lidocaine concentration. The effect appears immediately after lidocaine administration and rapidly diminishes as the blood lidocaine concentration decreases. The rapid decrease in the lidocaine plasma level could explain why Bacaner\textsuperscript{19} failed to observe a change in the ventricular fibrillation threshold when tested 30 min after drug administration. As observed in the present study, as well as in others,\textsuperscript{15} the ability of lidocaine to elevate the fibrillation threshold is of short duration after a single bolus injection. The effects of methyl lidocaine on the ventricular fibrillation threshold are consistent with our observations on another quaternary ammonium compound, dimethyl propranolol,\textsuperscript{20} and suggest that the quaternary structure is effective in increasing the threshold for electrical fibrillation. The quaternary ammonium compound, unlike the secondary or tertiary ammonium compounds, do not exert their effects immediately. As observed in the present study, the effect of methyl lidocaine on the ventricular fibrillation threshold was maximal at 1 to 3 hr after administration. Part of this delay may be related to a decrease in the rate at which a charged molecule crosses the myocardial cell membrane. On the other hand this same phenomenon might account for the long duration of action of the quaternary derivative as compared to the tertiary lidocaine.

The present studies confirm those reported recently by Gillis et al.\textsuperscript{13} and in addition, demonstrate the effectiveness of methyl lidocaine against digitalis-induced arrhythmias as well as its ability to increase the ventricular fibrillation threshold. The fact that the quaternary ammonium derivative does not significantly affect the central nervous system and possesses a longer duration of action certainly suggests distinct advantages for this drug over its parent compound, lidocaine. As proposed by Lucchesi and Iwami\textsuperscript{21} and Schuster et al.\textsuperscript{22} the quaternary ammonium salts provide an excellent means of limiting the pharmacological activity of antiarrhythmic drugs to effects on the electrophysiological properties of the heart.
References


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