

Comparison of Methyllidocaine and Lidocaine on Arrhythmias Produced by Coronary Occlusion in the Dog

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SUMMARY

Methyllidocaine, a quaternary ammonium derivative of lidocaine, was tested as a treatment for the ventricular ectopic beats occurring in unanesthetized dogs 24 hours after two-stage ligation of the anterior descending branch of the left coronary artery. The electrocardiogram (lead II) and electroencephalogram were recorded. Methyllidocaine (4 and 8 mg/kg) injected i.v. during a 1-min period produced a significant reduction in ectopic beats with no significant increase in EEG activity. Lidocaine (4 and 8 mg/kg) administered similarly caused similar antiarrhythmic effects but produced a significant increase in EEG activity. A dose of 8 mg/kg caused tonic-clonic seizures in three of five dogs. Both drugs were also given i.v. (15 mg/kg) to unanesthetized cats. Methyllidocaine did not induce convulsions in four of four animals whereas lidocaine induced convulsions in three of three animals. It is concluded that methyllidocaine is as effective an antiarrhythmic agent as lidocaine but does not possess the central nervous system excitatory actions observed with lidocaine.

Additional Indexing Words:

Convulsions

Electroencephalogram

Potency comparison

THE LOCAL anesthetic, lidocaine, is recognized as the drug of choice for the treatment of ventricular extrasystoles and ventricular tachycardia occurring after myocardial infarction.¹ Its effectiveness as an antiarrhythmic agent has been documented in a number of studies in animals²⁻⁵ and humans.⁶⁻¹² The widespread use of lidocaine is based on these findings and on the fact that it has less depressant effects on cardiac contractile force and cardiac conduction than other antiarrhythmic drugs,¹³ and that it has a rapid onset of action.¹⁴

Although lidocaine is relatively nontoxic to the cardiovascular system when compared to other antiarrhythmic drugs, it is neurotoxic. Its neural effects are manifested through the central nervous system and may culminate in generalized convulsions and death.^{7, 15-17} Less serious neural effects

ascribed to the drug are paresthesias, drowsiness, vertigo, confusion, tinnitus, and blurred vision.¹⁸ This neurotoxicity is the factor which limits the use of the drug. Recently a quaternary ammonium derivative of lidocaine, methyllidocaine, has been described which exerts an identical degree of local anesthetic activity,¹⁹ and apparently does not produce the seizures and spasticity seen in animals receiving lidocaine.²⁰ The present study was designed to determine whether methyllidocaine would suppress ventricular arrhythmias following coronary occlusion without producing an excitatory effect in the central nervous system.

Methods

Dogs unselected as to age or sex and ranging from 16 to 22 kg in weight were anesthetized by an intravenous injection of pentobarbital sodium (30 mg/kg). Mechanical ventilation with room air was instituted through a cuffed endotracheal tube. Under sterile conditions the heart was exposed through the fourth left intercostal space and the pericardium incised. The anterior descending branch of the left coronary artery was dissected for a short length at a level about 1 cm distal to the left atrial appendage and occluded in two stages according to the method described by Harris.²¹ The chest was closed and a polyethylene catheter for injecting drugs was inserted into the jugular vein and exteriorized at the nape of the neck.

Animals were studied the following day in the unanesthetized state. All animals had been trained

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previously (i.e. before surgery) to lie quietly while ECG recordings (lead II) were made. The electroencephalogram was recorded from standard EEG needle electrodes placed biparietally so that the needle tip entered obliquely and rested on the parietal bone. The low and high filters were set at 0.3 and 30 Hz, respectively. The EEG and ECG were displayed continuously on two channels of a polygraph. Preoperative electrocardiograms demonstrated sinus rhythm in all animals with heart rates ranging from 70 to 150 beats/min (average 116.2 ± 6.4). Twenty-five to 32 hours after occlusion, the ECG revealed ventricular ectopic beats of multifocal origin. This arrhythmia was quantitated by counting every beat during a 5-min period and noting the number which were of abnormal and normal origin.³ A minimum of two 5-min counting periods was obtained before the first dose of drug was administered. Both methylidocaine and lidocaine were used in solutions of 20 mg/ml, and doses of 4 and 8 mg/kg were tested. These doses were chosen because studies of others^{3,5} indicate that 2.5–10 mg/kg of lidocaine is necessary in order to demonstrate any sort of an effect of the drug on arrhythmias produced by coronary occlusion in the dog. The smallest dose was always given first with at least a 30-min interval between injections. The drugs were infused through the jugular vein catheter over a 1-min period and the catheter flushed rapidly with 5 ml of saline. Controls for all drug injections were obtained by infusing the same volume of saline and flushing the catheter rapidly with 5 ml of saline.

The effects of methylidocaine and lidocaine were also studied in cats. Observations were made before and after rapid i.v. administration of 15 mg/kg to unanesthetized animals.

The following drugs were used: methylidocaine iodide* (solutions were freshly prepared by dissolving the powder in 0.85% sodium chloride solution); lidocaine hydrochloride† (obtained as the sterile aqueous solution which contains 0.6% sodium chloride and 0.1% methylparaben); and pentobarbital sodium.‡ The doses of the drugs were calculated as their salts.

Results

The effect of methylidocaine in doses of 4 and 8 mg/kg on arrhythmias produced by coronary occlusion was studied. The data are summarized in table 1. The lower dose produced a significant reduction in the number of abnormal beats and also caused a significant degree of cardiac slowing. The onset of action occurred an average of 1.4 ± 0.28

(SE) min after the beginning of the injection. The peak effect (as indicated by peak heart rate slowing or occurrence of the greatest number of sinus beats) was reached 3.6 ± 0.77 min after the beginning of injection. The duration of action varied from 15 min to more than 30 min. In one of the seven experiments, the effect wore off at 15 min; in the rest, the effect persisted longer than the 30-min period of observation.

The EEG recordings showed no alteration of activity after administration of methylidocaine. Two of the seven animals did exhibit other signs of an extracardiac nature. These were licking and swallowing as well as hyperventilation.

The higher dose of methylidocaine produced a significant reduction in the number of abnormal beats as well as a significant increase in the number of sinus beats (table 1). Heart rate decreased but the change was not significant. Time to onset was 1.7 ± 0.70 min, and peak effect was reached 5.3 ± 1.5 min after the beginning of injection. In each case, the effect persisted longer than the 30-min observation period. EEG activity increased in two of the five dogs while no change was noted in the other three animals. Convulsions did not occur in any of the animals. Only four dogs are included in table 1 because one dog died of ventricular fibrillation 2 min after the drug injection had started. In that animal, methylidocaine had converted the abnormal rhythm to sinus rhythm within 1 min after the start of injection. Sinus rate was 130 beats/min and then jumped to 155 beats/min, and the heart unexpectedly fibrillated. Three of the five animals seemed agitated and excited. Hyperventilation was also noted. Licking and swallowing movements were observed in two of the five dogs. These effects occurred from 15 sec to 6 min after the start of injection and usually disappeared within 10 min from the time of injection.

An experiment demonstrating the effect of 8 mg/kg of methylidocaine on the ECG and the EEG appears as figure 1. Multifocal ventricular ectopic beats were present before the drug was administered. After methylidocaine, there was complete suppression of the arrhythmia with restoration of sinus rhythm at a slower rate than the ventricular rhythm. No change in EEG activity can be noted. Conversion to sinus rhythm was total, and persisted for more than 30 min after the drug had been administered.

Comparative results obtained with lidocaine are summarized in table 2. While the lower dose

*Lidocaine base was generously supplied by Dr. G. Vinton Hallock of Astra Pharmaceutical Products, Inc., Worcester, Massachusetts. The methylidocaine was synthesized from it by Dr. Thomas Mittag, Department of Pharmacology, Mount Sinai School of Medicine, New York, New York.

†Astra Pharmaceutical Products, Inc., Worcester, Massachusetts.

‡Abbott Laboratories, North Chicago, Illinois.

Table 1

Effect of Methyllidocaine on Arrhythmias Produced by Coronary Occlusion

Experiment no.	Dose (mg/kg)	Before drug			After drug		
		No. of abnormal beats/5 min	No. of sinus beats/5 min	Heart rate (beats/min)	No. of abnormal beats/5 min	No. of sinus beats/5 min	Heart rate (beats/min)
1	4	948	0	190	840	15	171
2	4	907	0	181	670	130	160
3	4	640	6	129	74	553	125
4	4	851	0	170	804	0	161
5	4	959	0	192	867	14	176
6	4	679	5	137	119	452	114
7	4	770	24	159	17	655	134
Mean ± SE		822 ± 48.6	5.0 ± 3.3	165 ± 9.4	484 ± 148.8*	260 ± 107.3	149 ± 9.1*
8	8	851	16	173	12	813	165
9	8	765	0	153	607	83	138
10	8	743	31	155	14	631	129
11	8	629	5	126	1	620	124
Mean ± SE		747 ± 45.7	13.0 ± 6.8	152 ± 9.7	158 ± 149.5*	537 ± 157.6*	139 ± 9.1

*P < 0.05 with paired comparisons.

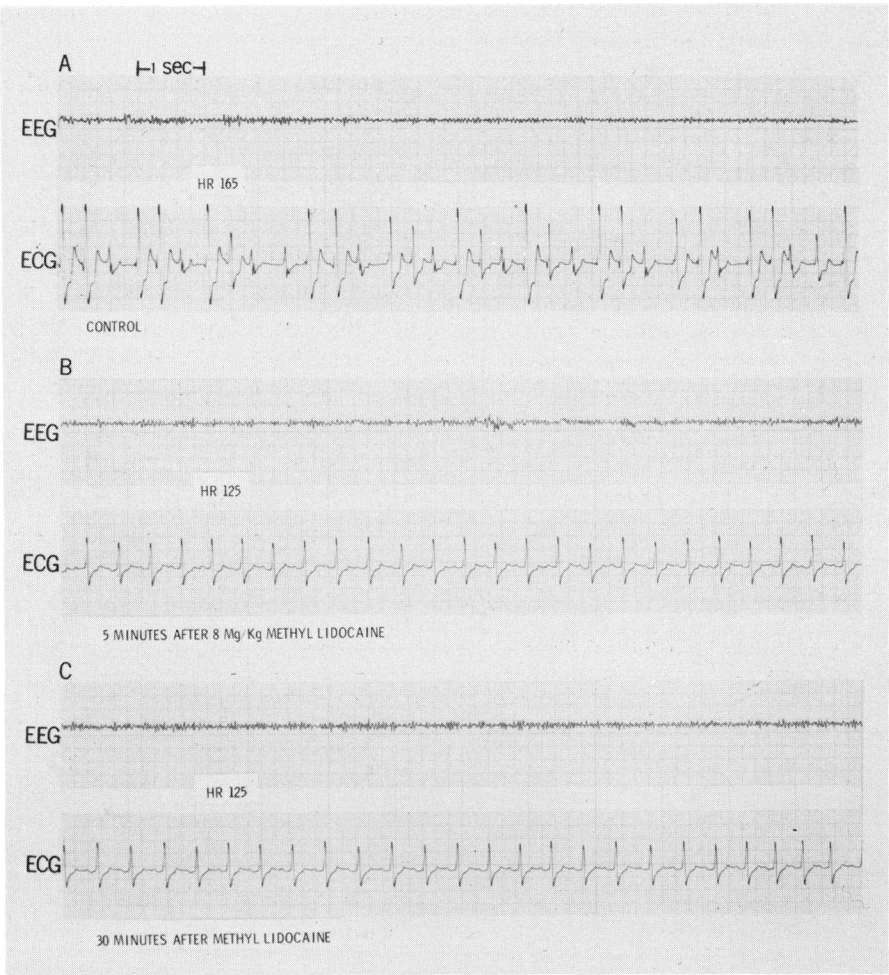


Figure 1

Effects of methyllidocaine on multifocal ventricular tachycardia induced by coronary occlusion. (A) Electroencephalogram (EEG) and electrocardiogram (ECG) tracings before the administration of methyllidocaine. (B and C) EEG and ECG effects after an 8 mg/kg i.v. dose of methyllidocaine.

decreased the number of abnormal beats and the heart rate, these effects were not statistically significant. In two of the five animals, an increase in EEG activity occurred; one of these became very excited and had to be restrained. Hyperventilation occurred in three of the animals.

The higher dose of lidocaine produced a significant reduction in the number of abnormal beats but did not produce a significant change in the number of sinus beats or in the heart rate (table 1). The time of onset was 1.0 ± 0.15 min, and peak effect was 2.2 ± 0.25 min after the start of injection. The duration of action ranged from 7.0 to 31.0 min with a mean of 15.6 ± 4.1 min. Enhancement in the EEG activity was observed in all five animals. Tonic convulsions occurred in three of the five dogs between 1.5 and 2.0 min after the start of the lidocaine injections. All animals survived, but either abnormal beats became numerous during the time of convulsions or an overdrive mechanism became apparent (fig. 2). Preconvulsive twitching movements were noted in the other two animals. Finally, postictal depression was prominent in two of the three dogs that convulsed; EEG activity was markedly decreased in both animals.

An experiment demonstrating the effect of 8 mg/kg of lidocaine on the ECG and EEG appears as figure 2. Multifocal ventricular ectopic beats were present before the drug was administered. At $1\frac{1}{2}$ min after the start of the lidocaine injection conversion to sinus rhythm was noted; the sinus rate, however, was 35 beats faster than the abnormal rate and hence may have been due to overdrive suppression of the ventricular pacemakers. At this time, the dog was phonating, defecating,

and convulsing. Evidence of the latter can be seen from the EEG trace. At 3 min, the convulsion had stopped, and sinus rhythm persisted but at a rate slower than the abnormal rate, indicating a depressant effect of lidocaine on automaticity. Effects of lidocaine on cardiac rhythm and EEG activity were over by 30 min.

The data summarized in tables 1 and 2 suggest that methyllidocaine might be more potent than lidocaine in reducing the number of ventricular ectopic beats. As another means of comparison, the regression equation for the relationship between the effect of the drug and the dose was calculated (fig. 3). From the regression lines, an approximation of the effective dose for producing a 50% effect can be obtained. These doses are 14 and 40 μ mole/kg for methyllidocaine and lidocaine, respectively. It appears from this type of evaluation that methyllidocaine is about three times more potent than lidocaine. However, with the small number of experiments performed, and with the great variability in response from animal to animal, the difference in potency did not achieve statistical significance.

Both drugs were also tested for convulsive activity using a dose of 15 mg/kg given intravenously to unanesthetized cats. Methyllidocaine did not induce convulsions in four of four animals whereas lidocaine induced convulsions in three of three animals. The convulsions were tonic and lasted 2–3 min; each animal recovered. The four animals treated with methyllidocaine were ataxic and were unable to support their body weight indicating probable muscle weakness. Breathing

Table 2

Effect of Lidocaine on Arrhythmias Produced by Coronary Occlusion

Experiment no.	Dose (mg/kg)	Before drug			After drug		
		No. of abnormal beats/5 min	No. of sinus beats/5 min	Heart rate (beats/min)	No. of abnormal beats/5 min	No. of sinus beats/5 min	Heart rate (beats/min)
1	4	983	0	197	939	0	188
2	4	672	108	156	498	265	153
3	4	926	0	185	788	71	172
4	4	780	0	156	766	0	153
5	4	654	48	140	126	569	139
Mean \pm SE		803 \pm 66.1	31.2 \pm 21.3	167 \pm 10.5	623 \pm 143.2	181 \pm 108.4	161 \pm 8.5
6	8	958	0	192	866	48	183
7	8	765	52	163	271	479	150
8	8	838	0	168	451	315	150
9	8	639	66	141	61	687	150
10	8	893	37	186	721	96	163
Mean \pm SE		819 \pm 55.0	31.0 \pm 13.5	170 \pm 9.0	474 \pm 146.1*	325 \pm 119.2	159 \pm 6.5

* $P < 0.05$ with paired comparisons.

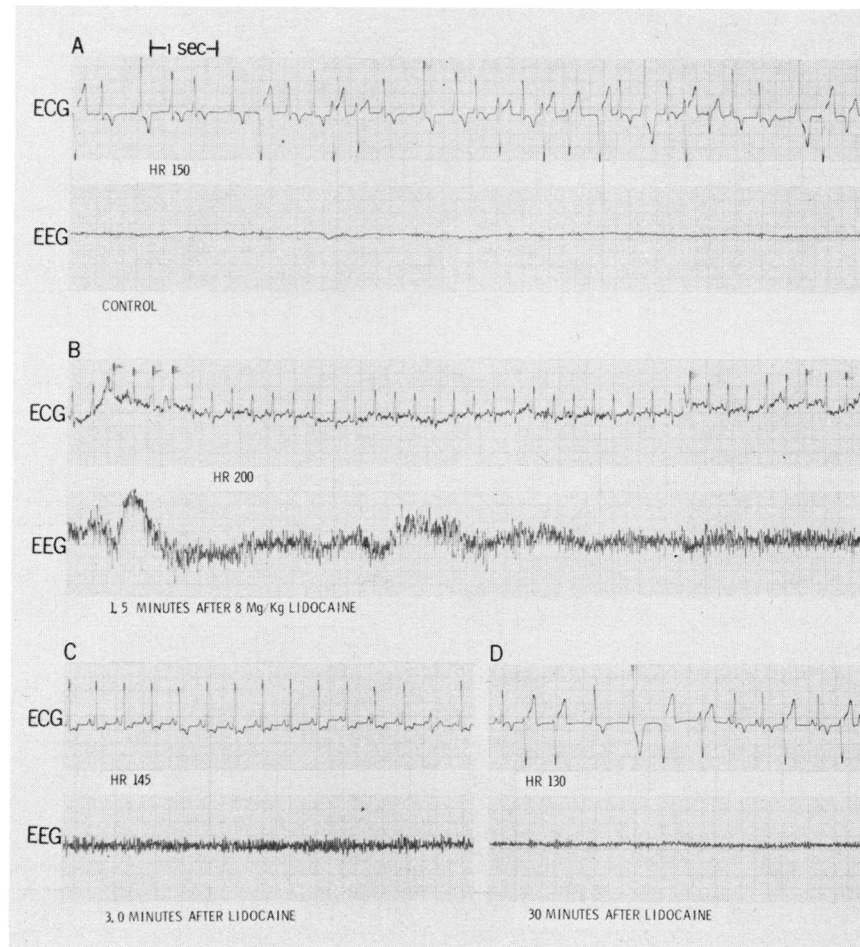


Figure 2

Effects of lidocaine on multifocal ventricular tachycardia induced by coronary occlusion. (A) Electrocardiogram (ECG) and electroencephalogram (EEG) tracings before the administration of lidocaine. (B, C, and D) ECG and EEG effects after an 8 mg/kg i.v. dose of lidocaine. Note the increase of EEG activity in B; this was associated with tonic convulsions (see text).

was labored but adequate and excessive bronchial secretion was noted; all animals survived.

Discussion

The purpose of this study was to determine whether methyllidocaine has the capacity to counteract ventricular arrhythmias produced by coronary occlusion. The results indicate that methyllidocaine is an effective antiarrhythmic substance. The drug was at least as effective, and perhaps more effective, than lidocaine in the treatment of ventricular rhythm disturbances. Moreover, its effect was not accompanied by convulsive activity.

Although lidocaine has been shown to be a convulsant material in animals and man,²² it has been suggested that methylparaben (the preserva-

tive in the lidocaine solution) may cause convulsions.²³ This does not seem to be a pharmacologic property of methylparaben.^{24, 25} Methylparaben appears to be relatively innocuous and has an LD₅₀ in dogs of about 940 mg/kg when given intravenously at the rate of 20 mg/kg/min,²⁵ a rate 50 times faster than employed in the present study. Moreover, toxicity associated with intravenously administered methylparaben is not associated with convulsive activity, but with myocardial depression and hypotension. Thus it appears to be the lidocaine rather than the preservative contained in the commercial preparation which is responsible for convulsions.

The greater apparent potency of methyllidocaine may be due to a difference in its volume of

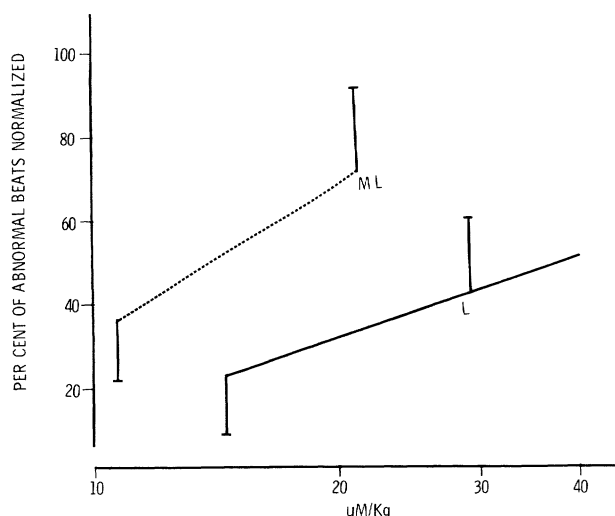


Figure 3

Estimates of the regression equations for the relationship between the effects of methylidocaine (ML) and lidocaine (L) on ventricular ectopic beats induced by coronary occlusion and the doses of each drug. Each point represents the average response of four to seven dogs. The vertical bars on the regression lines indicate standard errors. Values for the vertical axis were obtained by dividing the number of new sinus beats that were present during the 5-min post-drug period by the number of ectopic beats that were present during the 5-min predrug period. The scale on the abscissa for dose is logarithmic.

distribution. Methylidocaine, being a quaternary ammonium compound, exists in solution only as the cationic form.²⁶ Cations, due to their charge, have great difficulty penetrating lipid membranes. Lidocaine is a tertiary amine with a pK_a of 7.9; it therefore exists both as uncharged (about 30%) and charged (about 70%) molecules at physiologic pH . The uncharged form has a high degree of lipid solubility and can readily penetrate lipid membranes. It therefore would be expected that lidocaine is more widely distributed into body compartments and hence results in a reduced drug concentration at the various sites where it acts. This suggestion is supported by findings that lidocaine enters the central nervous system and produces tonic convulsions. Methylidocaine produced no convulsions, suggesting little distribution of drug to the central nervous system.

The antiarrhythmic effect of methylidocaine also persisted for a longer time than that of lidocaine. According to numerous studies,^{1, 3, 5, 6, 8, 27} lidocaine has a very short duration of action (10–20 min) which agrees with our findings. The short duration is related to an oxidative deethylation and hydrolysis by a hepatic microsomal enzyme system.^{28, 29} To

reach these enzymes a drug must be lipid soluble. Thus methylidocaine would not have access to these enzymes, and the unmetabolized form would be present in the body for a longer period of time.

The possibility exists that the antiarrhythmic effect of methylidocaine may be due to a rapid conversion to lidocaine in the body. However, this seems unlikely, since methylidocaine was found to be more potent than lidocaine and did not possess convulsive properties. Oppenheim⁹ also considered and rejected the possibility that methylidocaine was being transformed to lidocaine.

As mentioned above, both methylidocaine and lidocaine exert an identical degree of local anesthetic activity; equivalent doses of each produce equivalent neurodepressant activity on the unmyelinated nerve terminal of the cat soleus muscle.¹⁹ Since both agents depress neural activity to skeletal muscle, it is conceivable that both drugs depress neural activity to the heart, and this may be the mechanism of their antiarrhythmic action. This postulate is consistent with the large body of data that has accumulated which implicates the nervous system as a causative factor in the development of ventricular arrhythmias following coronary occlusion.^{30–38} In addition, lidocaine has been reported to decrease automaticity in isolated canine Purkinje fibers.³⁹ This may contribute to its antiarrhythmic action, as anoxia has been shown to increase the rate of phase-4 depolarization in Purkinje fibers.⁴⁰

In summary, the present study indicates that methylidocaine is at least as good and probably a better antiarrhythmic drug than lidocaine when tested against the coronary ligation arrhythmia. The quaternary ammonium derivative seems to lack the prominent central nervous system effects of lidocaine which are the major limiting factors in the clinical use of the latter. These data indicate that methylidocaine has considerable promise as an antiarrhythmic agent and should be the subject of further study.

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