Synergistic Interaction between Class I Antiarrhythmic Drugs and Halothane in Depressant Effects on Ventricular Activation in a Canine Myocardial Infarction Model

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Previous studies have showed that halothane has depressed ventricular activation in a canine myocardial infarction model. It is also well known that class I antiarrhythmic drugs depress ventricular activation in the infarcted myocardium. In the present study, we examined whether some electrophysiologic interactions between halothane and two class I antiarrhythmic drugs, lidocaine and procainamide, occur in a canine myocardial infarction model. Halothane, lidocaine and procainamide prolonged the activation time in the infarcted zone, and the combination of halothane and either lidocaine or procainamide markedly prolonged the activation time or blocked the delayed activation in the infarcted zone. Although the mechanism of the interaction is not clear, the present results suggest a synergistic interaction between halothane and class I antiarrhythmic drugs. Therefore, care should be taken that doses of class I antiarrhythmic drugs during halothane anesthesia will not be an overdose.

Keywords halothane; class I antiarrhythmic drug; interaction; canine myocardial infarction; ventricular activation

When an anesthetic is administered to patients with ischemic heart disease, it may affect not only the hemodynamics, but also the electrophysiological properties of the ischemic myocardium. 2-11) Turner et al. 6) examined the effects of halothane on the electrical activities of Purkinje fibers derived from normal and infarcted canine hearts. They showed that halothane decreased the maximal rate of depolarization (V max), slowed the conduction and prolonged the effective refractory period in the infarcted zones. Ikemoto et al. reported that volatile anesthetics such as halothane or enflurane slowed ventricular conduction without any significant depression of V max in isolated guinea pig papillary muscle. 12) It is well known that class I antiarrhythmic drugs reduce V max and depress ventricular conduction. 13) An electrophysiologic interaction between halothane and quinidine has been observed in isolated canine Purkinje fibers. 14) Delayed ventricular conduction in infarcted myocardium play an important role in the occurrence of ventricular arrhythmias, and class I antiarrhythmic drugs cause their antiarrhythmic action partly by a block of the delayed conduction. 13) In the present study, we determined whether an electrophysiologic interaction between halothane and class I antiarrhythmic drugs, lidocaine and procainamide, occurs in a canine myocardial infarction model.

MATERIALS AND METHODS

Animal Preparation Mongrel dogs weighing between 8.0—13.0 kg were anesthetized with sodium pentobarbital, 30 mg/kg i.v. Each animal was intubated and ventilated with room air using a positive pressure respirator. A left thoracotomy was performed in the fourth intercostal space and the heart was exposed. After opening the pericardium, the left anterior descending coronary artery (LAD) was occluded according to Harris 15) and then several branches of LAD were also occluded. The chest was closed after the complete occlusion, and routine postoperative care was performed including prophylactic antibiotic therapy, i.e. daily intramuscular administration of postinfarction convalescence.

Measurement of the Ventricular Activation Time The effects of the drugs were examined in 16 animals. Five to eight days after the LAD occlusion, the animal was reanesthetized with sodium pentobarbital 20 mg/kg i.v.; this dose was slightly less for a deep anesthesia. Ventilation was performed at 12 times/min with 100% O2 at a tidal volume of 15 ml/kg. The body temperature of the animal was maintained at 36—37°C. A left thoracotomy was performed and the pericardium was opened. After the heart was cradled on the pericardium, bipolar stimulating electrodes were sutured on the left atrial appendage and right ventricle for atrial pacing and applied premature ventricular stimulation, respectively. For recording the ventricular activation, one electrode was sutured on the normal area in the right ventricle, and the other two were on the infarcted zone in the left ventricle, as previously reported. 11) The atrial pacing was performed at a rate slightly above the sinus rhythm in a control state throughout the electrophysiological study. The premature stimulation of the right ventricle was performed by a 5 ms rectangular with a stimulus strength triple the diastolic threshold. In order to study the effect of the drug on ventricular activation, the conduction time of the premature stimulation-induced ventricular excitation was measured in both the normal and infarcted zones of the ventricle. The time interval from the artifact of the premature stimulation to a sharp and reproducible deflection was measured on epicardial bipolar electrocardiograms, and this value was taken as the activation time. The premature stimulation was triggered by the excitation of the normal zone. The coupling interval of the stimulation was changed, usually between 320 and 140 ms. The effects of the two drugs were compared in the activation of the same area. The bipolar electrocardiogram was amplified at a filter frequency of 50 to 1000 Hz. Lead II ECG, femoral arterial pressure and the epicardial bipolar electrocardiograms were recorded on an 8 channel

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polygraphic recorder (Nihonkoden, Tokyo, Japan) at a
paper speed of 100 mm/s. The 16 animals were divided
into two groups (groups A and B). In group A, the effects
of halothane, lidocaine and the two combined were
examined, and in group B, the effects of halothane,
procainamide and the two combined were examined at
time interval of about an hour, when the effect of a
prior drug was almost negligible. Usually, the effects
of halothane were examined first, because the effect of this
drug disappeared more rapidly.

Drug Administration The concentration of halothane
was adjusted to maintain an endtidal concentration of
about 1 MAC (minimum alveolar concentration; the
equivalent MAC value for dogs is 0.9%). A similar
concentration was employed by other investigators. Inspi-
rotory and expiratory concentrations of halothane
were monitored with a gas analyzer (Engstrom EMMR,
IMI, Tokyo, Japan). In the present study, a concentration
of halothane of more than 1 MAC could not be examined
because of serious hypotension. Animals with myocardial
infarction were used in the present study, so serious hy-
potension was easily produced by the volatile anesthetic.
After achieving a steady state for 60 min, the measure-
ments for halothane were started. Lidocaine and procain-
amide were administered intravenously at doses of 3 and
5 mg/kg, respectively. The measurements were started
5 min after administration. At 20 min before the admin-
istration of the lidocaine or procainamide, an additional
3 mg/kg of sodium pentobarbital was administered to
maintain anesthesia.

Statistical Analysis All data were expressed as the
arithmetic means ± S.E.M. Statistical significance of
changes in the ventricular activation time after admin-
istration of the drug was determined by a paired t-test. The
Student's t-test was used for analysis of changes within
other parameters. The criterion for statistical significance
was p < 0.05.

Drugs The following drugs were used: halothane
(Takeda Pharmaceutical Co., Ltd., Osaka, Japan), lidoc-
aine hydrochloride (Fugisawa Pharmaceutical Co., Ltd.,
Osaka, Japan), procainamide hydrochloride (Daiichi
Pharmaceutical Co., Ltd., Tokyo, Japan).

RESULTS

Effects of the Drugs on the Blood Pressure and the Heart
Rate Table I summarizes the results in 14 animals.
Halothane 1 MAC significantly reduced blood pressure
in the two groups. Lidocaine and procainamide did not
significantly reduce blood pressure. Halothane plus lidoc-
aine or halothane plus procainamide significantly re-
duced blood pressure, but the reduction was not statis-

<table>
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<th>Table I. Effects of Halothane, Lidocaine, Procainamide and Their Combination on Mean Arterial Blood Pressure (mmHg)</th>
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<td>Group A</td>
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<td>Group B</td>
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Values are the mean ± S.E.M. of seven animals. a) p < 0.01 vs. control.

Fig. 1. Effects of Lidocaine 3 mg/kg, Halothane 1 MAC and Their Combination on Ventricular Activation

A, control; B, lidocaine; C, halothane; D, halothane + lidocaine. L-II: standard limb lead II ECG. NZeg, IZeg: electrocardiograms of the normal and the infarcted zones. The upwards arrows indicate premature stimulation with a coupling interval of 200 ms. The basic cycle length was 400 ms. The downwards arrows are delayed activations. The activation times in the infarcted zone were 85 ms in the control, 95 ms after lidocaine, 95 ms after halothane, and 160 ms after their combination.
Fig. 2. Effects of Lidocaine 3 mg/kg, Halothane 1 MAC and Their Combination on the Activation Time of Delayed Activation at Various Coupling Intervals
A: ischemic zone. B: normal zone. C: control; L: lidocaine 3 mg/kg; H: halothane 1 MAC; H+L: halothane plus lidocaine.

Fig. 3. Halothane Plus Lidocaine-Induced Block of Delayed Activation in the Infarcted Zone
A: control; B: lidocaine; C: halothane; D: halothane + lidocaine. L-II: standard limb lead II ECG. NZeg, IZeg: electrocardiograms of the normal and the infarcted zones. The upwards and downwards arrows indicate the premature stimulation with a coupling interval of 220 ms and delayed activation, respectively. The basic cycle length was 330 ms.

Iaturally different from that with halothane alone.

Interaction between Halothane and the Class I Antiarrhythmic Drugs in the Effect on Ventricular Activation
Representative electrocardiograms recorded from normal and infarcted zones of the ventricle are shown in Fig. 1 (control). At the basic cycle length, the electrocardiogram recorded from the normal zone consisted of deflections with a duration of less than 50 ms, whereas most of the electrocardiograms recorded from the infarcted zone were fractionated potentials, indicating delayed activation in the infarcted zone. The delayed activation was further delayed in the premature stimulation-induced excitation.

The effects of halothane 1 MAC, lidocaine 3 mg/kg and a combination of the two are shown in Fig. 1. Halothane alone or lidocaine alone slightly prolonged the activation time in the infarcted zone under premature excitation. Halothane plus lidocaine markedly prolonged the activation time of the delayed activation in the infarcted zone.

The effects of these drugs were dependent on the coupling interval of the premature excitation (Fig. 2). Further prolongation was observed at a shorter coupling interval. At coupling intervals more than 250 ms, the effect of halothane or lidocaine was negligible, but the combination of these drugs obviously prolonged the activation time. At coupling intervals between 180 and 250 ms, the effect of either drug alone was slight, yet their combination markedly prolonged the activation time.

Seriously delayed activation was more prominently affected by these drugs. In the case shown in Fig. 3, a combination of the two drugs produced a block of the delayed activation: A block of the delayed activation was observed in 2 of 8 animals with lidocaine, 1 of 8 animals...
TABLE II. Increases in the Ventricular Activation Time with Halothane, Lidocaine, Procainamide and Their Combination at a Coupling Interval of 200 ms in a Canine Myocardial Infarction Model

<table>
<thead>
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<th>Group A</th>
<th>Group B</th>
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<tr>
<td>Basal value (ms)</td>
<td>Basal value (ms)</td>
</tr>
<tr>
<td>Halothane</td>
<td>Lidocaine</td>
</tr>
<tr>
<td>Normal zone</td>
<td>14 ± 7</td>
</tr>
<tr>
<td>Infarcted zone</td>
<td>14 ± 7</td>
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Increases in the activation time are represented as % of the basal values (ms). Values are mean ± S.E.M. of seven animals. <sup>a</sup> p < 0.01 vs. control.

with halothane and 6 of 8 animals with a combination of the two drugs.

Table II summarizes the results of seven animals at a coupling interval of 200 ms. In these data, the activation which was blocked by the drug was not included. The prolongation of the activation time was about 16% with lidocaine, 14% with halothane and 65% with the two combined, respectively. At a coupling interval of 260 ms, prolongation of the activation time in seven animals was 5±4%, 7±3% and 31±6% (p<0.01) with lidocaine, halothane and a combination of the two, respectively. The effect of their combination on the activation time in the normal zone was slight. A synergistic interaction in the effect on delayed activation was similar observed between halothane and procainamide. Prolongation of the activation time was about 17% with procainamide, 12% with halothane and 63% with the two combined. The combination of halothane procainamide also increased the incidence of a block of delayed activation: A block was observed in 2 of 8 animals with procainamide and 2 of 8 animals with halothane, and in 6 of 8 animals when the two were combined.

DISCUSSION

The present study showed that halothane and lidocaine depressed delayed activation in infarcted zones of canine ventricles, which is consistent with the facts that both drugs depress $F_{max}$ in isolated cardiac muscle.12,16 The effects of halothane and lidocaine were similar, because they both selectively depressed the activation of infarcted zones and the effects were dependent on the coupling interval. However, several investigators suggested that the mechanisms involved in the effects of halothane and lidocaine on ventricular conduction may be different.12 A combination of lidocaine and halothane markedly depressed the delayed activation in the infarcted zone and frequently produced a block of this activation. The interaction between these drugs was synergistic.

An electrophysiological interaction between volatile anesthetics and antiarrhythmic drugs have been reported by only a small group of investigators. According to Gallagher et al., halothane and quinidine showed synergistic interaction with a decrease in action potential amplitude, increases in action potential duration, and a prolongation of conduction time in isolated canine Purkinje fibers.14 It has also been reported that volatile anesthetics are capable of decreasing the total hepatic blood flow and inhibiting the hepatic oxidative metabo-

lism of various drugs.17-20 According to Frink et al., halothane decreased hepatic blood flow and inhibited hepatic biotransformation of verapamil.20 Bentley et al., reported that halothane decreased the clearance of lidocaine, mainly by decreased hepatic blood flow and/or the inhibition of hepatic lidocaine metabolism.17

A synergistic interaction between halothane and lidocaine observed in the present study may be caused partly by a decrease in the hepatic metabolism of lidocaine, since hepatic metabolism largely contributes to the clearance of lidocaine.16 A synergistic interaction in the depressant effect on activation time was similarly observed between halothane and procainamide. The hepatic metabolism of procainamide occurred to a lesser extent.16 Thus, it is also probable that the interaction between halothane and lidocaine or procainamide may be partly attributed to an interaction involving in a direct electrophysiological effect of these drugs on the cell membranes of cardiac muscle.

Although the mechanism of interaction between halothane and the class I antiarrhythmic drugs is not clear, it is probable that inhalation of halothane may affect the antiarrhythmic effects of class I antiarrhythmic drugs. Because lidocaine and procainamide frequently produced a block of delayed activation during halothane anesthesia, the antiarrhythmic effects of these drugs may potentiated during halothane anesthesia. In contrast, a prolongation of ventricular activation time these drugs increased during halothane anesthesia. Therefore, it is also possible that the proarrhythmic effects of these drugs may be enhanced during halothane anesthesia. Obviously, then, care should be taken to ensure that a dose of a class I antiarrhythmic drug may not be an overdose during halothane anesthesia.

REFERENCES AND NOTES

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