Electrophysiologic Interaction between Class I Antiarrhythmic Drugs and Volatile Anesthetics in Depressant Effects on Ventricular Activation in a Canine Myocardial Infarction Model

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Received September 13, 1993 Accepted January 6, 1994

ABSTRACT—Previous studies showed that volatile anesthetics depressed ventricular delayed activation in a canine myocardial infarction model. It is well known that class I antiarrhythmic drugs depress the ventricular activation in the infarcted myocardium. In the present study, we examined the electrophysiologic interaction between volatile anesthetics (sevoflurane, isoflurane) and class I antiarrhythmic drugs (lidocaine, procainamide) in effects on the ventricular delayed activation in a canine myocardial infarction model. The conduction time of the premature stimulation-induced ventricular excitation was measured in both normal and infarcted zones of the ventricle. An interval from the premature stimulus artifact to the epicardial activation was measured on bipolar electrograms as an index of conduction time, i.e., activation time. In the infarcted zone, the volatile anesthetics and class I antiarrhythmic drugs prolonged the activation time in the infarcted zone, and the combination of the volatile anesthetics and the class I antiarrhythmic drugs markedly prolonged the activation time or blocked the delayed activation. In the normal zone, a similar synergistic interaction was observed, but the effect of these drugs was less compared with that in the infarcted zone. From these results, possible mechanisms to explain the synergistic interaction were discussed.

Keywords: Antiarrhythmic drug (class I), Volatile anesthetic, Myocardial infarction (canine), Ventricular activation

Many investigators reported that volatile anesthetics affect not only the hemodynamics, but also the electrophysiologic properties in ischemic myocardium (1–9). Turner et al. (5) 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 (Vmax), slowed the conduction and prolonged the effective refractory period in the infarcted zones. On the other hand, Ozaki et al. reported that volatile anesthetics such as halothane or enflurane slowed ventricular conduction without any significant depression of Vmax in isolated guinea pig papillary muscle (10). It is well known that ventricular delayed conduction in infarcted myocardium plays an important role in the occurrence of reentrant ventricular arrhythmias and that class I antiarrhythmic drugs cause their antiarrhythmic actions partly by a block of the delayed conduction (11). Gallagher et al. (12) have observed an electrophysiologic interaction between halothane and quinidine in isolated canine Purkinje fibers. They found a synergistic interaction between these drugs on action potential amplitude, action potential duration and conduction time. Previously, we showed that a depressant effect of lidocaine or procainamide on ventricular delayed conduction in canine myocardial infarction is enhanced during halothane anesthesia (13). In the present study, we examined the electrophysiologic interaction between class I antiarrhythmic drugs (lidocaine and procainamide) and volatile anesthetics (sevoflurane and isoflurane) in their effects on ventricular delayed activation 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 at 30 mg/kg, i.v. Each animal was intubated and ventilated with room air using a positive pressure respirator. A left thoracotomy
Measurement of the ventricular activation time

The effects of the drugs were examined in 19 animals. Five to eight days after the LAD occlusion, the animal was reanesthetized with sodium pentobarbital at 20 mg/kg, i.v.; this dose was slightly less than that 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 using an electric blanket. 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 applying a ventricular premature stimulation, respectively. Several bipolar electrodes were also sutured on the epicardial surface of the left or the right ventricle for recording the ventricular activation. Usually, 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. One of the electrodes in the infarcted zone was located in the area where a markedly delayed activation was recorded. Another electrode in the infarcted zone was located in any point within the infarcted area regardless of activation delay. The atrial pacing was performed at a rate slightly above the sinus rhythm in a control state throughout the electrophysiological study (171 ±7, n=19). The premature stimulation of the right ventricle was performed by a 5-msec rectangular pulse with a stimulus strength equal to the triple diastolic threshold. To study the effect of the drug on the ventricular activation, the conduction time of the premature stimulation-induced ventricular excitation was measured in both 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 the epicardial bipolar electrocardiograms, and this value was taken as the conduction time. We used the term “activation time” instead of “conduction time”, because these excitations do not always conduct to other areas. The premature stimulation was triggered by the excitation of the normal zone. The coupling interval of the stimulation was varied, usually between 320 and 140 msec. The effects of a single drug alone and the combination of two drugs were compared in the activation of the same area in each animal. 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 polygraphic recorder (Nihon Kohden, Tokyo) at a paper speed of 100 mm/sec. The 19 animals were divided into three groups (groups A, B and C). In group A (n=7), the effects of sevoflurane, lidocaine and their combination; in group B (n=6), the effects of sevoflurane, procainamide and their combination; and in group C (n=6), the effects of isoflurane, lidocaine and their combination were examined at a time interval of about hr when the effect of a prior drug was almost negligible. Usually the effect of the volatile anesthetics was first examined, because the effect of the drug disappeared more rapidly.

Drug administration

The concentration of sevoflurane or isoflurane was adjusted to maintain the end-tidal concentration at about 1 MAC (minimum alveolar concentration, equivalent MAC value for the dogs is 2.4% with sevoflurane and 1.5% with isoflurane). A similar concentration was employed by other investigators (9). Inspiratory and expiratory concentrations of halothane were monitored with a gas analyzer (Engstrom EMMR; IMI, Tokyo). In the present study, a concentration of the volatile anesthetics more than 1 MAC could not be examined because of serious hypotension. The animals with myocardial infarction were used in the present study, so serious hypotension was easily produced by the volatile anesthetics. After achieving a steady state for 60 min, the measurements for the volatile anesthetic were started. Lidocaine and procainamide were administered intravenously at doses of 3 and 5 mg/kg, respectively. In the present study, relatively low doses of the antiarrhythmic drugs were used, because synergism between these drugs and volatile anesthetics was expected. The measurements were started 5 min after the administration. At 20 min before the administration of the lidocaine alone or procainamide alone, additional sodium pentobarbital at 3 mg/kg was administered to maintain anesthesia.

Statistical analysis

All data were expressed as arithmetic means ± S.E.M. The statistical significance of changes in the ventricular activation time or blood pressure after the drug was determined by the paired t-test. The criterion for statistical significance was P < 0.05.

Drugs

The following drugs were used: sevoflurane (Maruishi Pharmaceutical Co., Ltd., Osaka), isoflurane (Dainippon Pharmaceutical Co., Ltd., Osaka), lidocaine hydro-
chloride (Fujisawa Pharmaceutical Co., Ltd., Osaka), and procainamide hydrochloride (Daiichi Pharmaceutical Co., Ltd., Tokyo).

RESULTS

Effects of the drugs on blood pressure

Table 1 summarizes the blood pressure of 19 animals.

Table 1. Effects of class I antiarrhythmic drugs (lidocaine, procainamide) and volatile anesthetics (sevoflurane, isoflurane) and their combination on mean arterial blood pressure (mmHg)

| Group  | Control  | Sevoflurane | Lidocaine | Sevoflurane + Lidocaine |
|--------|----------|-------------|-----------|-------------------------|
| A      | 126 ± 3  | 100 ± 3**   | 120 ± 4   | 98 ± 3**                |
| B      | 130 ± 7  | 95 ± 5**    | 121 ± 5   | 97 ± 5**                |
| C      | 118 ± 5  | 93 ± 3**    | 120 ± 5   | 90 ± 4**                |

Values are the means ± S.E.M. of 7 (group A) or 6 (groups B and C) animals. **P < 0.01 vs. control.

The volatile anesthetics at 1 MAC significantly reduced the blood pressure. Lidocaine alone or procainamide alone did not significantly reduce the blood pressure. The volatile anesthetic plus lidocaine or procainamide significantly reduced the blood pressure, but the reduction was not statistically different from that with the volatile anesthetic alone.

Fig. 1. Effects of lidocaine at 3 mg/kg, sevoflurane at 1 MAC and their combination on the ventricular activation. L-II: standard limb lead II ECG. NZeg, IZeg: electrocardiograms of the normal and the infarcted zones, respectively. The upward and downward arrows indicate the premature stimulation with a coupling interval of 200 msec and delayed activation, respectively. The basic cycle length was 400 msec. The activation times in the infarcted zone were 105 msec in the control, 115 msec after lidocaine, 115 msec after sevoflurane and 210 msec after their combination.
Interaction between volatile anesthetics and the class I anti-arrhythmic drugs in the effects on ventricular activation

Representative electrograms recorded from normal and infarcted zones of the ventricle are shown in Fig. 1. At the basic cycle length, control electrograms recorded from the normal zone consisted of deflections with a duration of less than 50 msec, whereas most of the electrograms recorded from the infarcted zone showed fractionated

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**Fig. 2.** Effects of lidocaine at 3 mg/kg, sevoflurane at 1 MAC and their combination on the activation time of the delayed activation at various coupling intervals. C: control, L: lidocaine at 3 mg/kg, S: sevoflurane at 1 MAC, S+L: sevoflurane plus lidocaine.

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**Fig. 3.** Sevoflurane plus procainamide-induced block of delayed activation in the infarcted zone. L-II: standard limb lead II ECG. NZeg, IZeg: electrocardiograms of the normal and the infarcted zones, respectively. The upward and downward arrows indicate the premature stimulation with a coupling interval of 220 msec and delayed activation, respectively. The basic cycle length was 450 msec. The activation times in the infarcted zone were 120 msec in the control, 144 msec after sevoflurane and 136 msec after procainamide. The open arrow indicates a block of the delayed activation.
The effects of these drugs were dependent on the coupling interval of the premature excitation. A typical case is shown in Fig. 2. More prolongation was observed at a shorter coupling interval. In the infarcted zone, sevoflurane alone and lidocaine alone prolonged the activation time by 10 msec in the premature excitation, whereas sevoflurane plus lidocaine prolonged the activation time by 105 msec. In the normal zone, a combination of the two drugs prolonged the activation time only by 14 msec.

Table 2. Increases in the ventricular activation time (msec) and the incidence of block (numbers of animals) with class I antiarrhythmic drugs (lidocaine, procainamide) and volatile anesthetics (sevoflurane, isoflurane) and their combination in a canine myocardial infarction model

| Group A | Basal value | Sevoflurane | Lidocaine | Sevoflurane + Lidocaine |
|---------|-------------|-------------|-----------|------------------------|
| Normal zone | 43 ± 3      | 13 ± 4      | 7 ± 3     | 26 ± 7*                |
| Infarcted zone | 110 ± 3     | 18 ± 4*     | 18 ± 4*   | 86 ± 11**              |
| Incidence of block | 1           | 1           | 4         |                        |

| Group B | Basal value | Sevoflurane | Procainamide | Sevoflurane + Procainamide |
|---------|-------------|-------------|--------------|-----------------------------|
| Normal zone | 38 ± 6      | 7 ± 3       | 5 ± 3        | 13 ± 4*                     |
| Infarcted zone | 109 ± 9     | 22 ± 4**    | 13 ± 4*     | 89 ± 4**                   |
| Incidence of block | 1           | 1           | 4         |                            |

| Group C | Basal value | Isoflurane | Lidocaine | Isoflurane + Lidocaine |
|---------|-------------|------------|-----------|-----------------------|
| Normal zone | 37 ± 4      | 4 ± 3      | 5 ± 2     | 14 ± 3*               |
| Infarcted zone | 118 ± 10    | 11 ± 3*    | 18 ± 4*   | 67 ± 5**              |
| Incidence of block | 0           | 1          | 3         |                       |

Values are the means ± S.E.M. of 7 (group A) or 6 (groups B and C) animals. *P < 0.05, **P < 0.01 vs. basal value. The incidence of block is the number of animals in which a block was observed.

The present study showed that volatile anesthetics and class I antiarrhythmic drugs depressed the delayed activation in infarcted zones of canine ventricles, which is consistent with previous results (5, 15, 16). In the Table 2, the effects of the drugs on the incidence of block are summarized. At coupling intervals between 200 and 320 msec, a block of the delayed activation was observed in 0 or 1 animal of each group with a single drug, whereas a block was observed in 3 or 4 animals with a combination of the antiarrhythmic drug and the anesthetic.

The effects of these drugs on the activation time at a coupling interval of 200 msec are also summarized in Table 2. In these data, the activation that was blocked by the drug was not included. In the infarcted zone, the prolongation of the activation time in group A was about 16% with lidocaine, 16% with sevoflurane and 78% with their combination. In group B, the prolongation was 20% with sevoflurane, 12% with procainamide and 82% with their combination. In group C, the prolongation of the activation time was 15% with lidocaine, 9% with isoflurane and 57% with their combination. In the normal zone, the prolongations of the activation time with the combination of these drugs were slight but statistically significant in the three groups.

DISCUSSION

The present study showed that volatile anesthetics and class I antiarrhythmic drugs depressed the delayed activation in infarcted zones of canine ventricles, which is consistent with previous results (5, 15, 16). In the present study, the effects of sevoflurane and isoflurane were examined, because these are now frequently used. The effects
of the volatile anesthetics and the class I antiarrhythmic drugs were similar, because these selectively depressed the activation of infarcted zones, and the effects were dependent on a coupling interval. Many investigators reported that class I antiarrhythmic drugs selectively depress the delayed conduction in the infarcted zone. According to Turner et al., halothane decreases the $V_{\text{max}}$ in the isolated Purkinje fibers of the infarcted zone, whereas it does not decrease the $V_{\text{max}}$ in the non-infarcted zones (5). Ikemoto et al. reported that halothane depresses the sodium currents of cardiac muscles and shifts the steady state inactivation curve in a negative direction along the potential axis (17). Sevoflurane and isoflurane may have similar effects, which may cause a selective depression of delayed conduction in the infarcted zone. However, several investigators suggested that mechanisms of the effects of the volatile anesthetics and class I antiarrhythmic drugs on ventricular conduction may be different (10, 17, 18). Ozaki et al. reported that halothane and enflurane depressed the conduction velocity without depressing $V_{\text{max}}$ in isolated guinea pig papillary muscle (10). Terrar and Victory showed that halothane depressed cell-to-cell electrical coupling (18). Spray and Burt reported that a variety of lipophilic molecules including halothane and myoplasmic acidification reduce cell-to-cell electrical coupling (19). Niggli et al. and others also reported a similar effect of volatile anesthetics on cell-to-cell electrical coupling (20, 21). According to Gardner et al., a damage in cell-to-cell or fiber-to-fiber electrical coupling may largely contribute to depressed conduction in myocardial infarction (22). Therefore, sevoflurane and isoflurane may have depressant effects on cell-to-cell electrical coupling, which may result in a depression of delayed activation.

A combination of lidocaine and sevoflurane or isoflurane 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 electrophysiologic interaction between volatile anesthetics and antiarrhythmic drugs has been reported by only a few groups of investigators. According to Gallagh er et al., halothane and quinidine showed synergistic interaction on a decrease in action potential amplitude, increases in action potential duration and prolongation of conduction time in isolated canine Purkinje fibers (12).

It has also been reported that volatile anesthetics are capable of decreasing total hepatic blood flow and inhibiting hepatic oxidative metabolism of various drugs (23–26). Bentley et al. reported that halothane decreased the clearance of lidocaine mainly by a decreased hepatic blood flow and/or inhibition of hepatic lidocaine metabolism (23). Although the effects of sevoflurane or isoflurane on hepatic biotransformation may be to a less extent compared to those of halothane (27, 28), the synergistic interaction between the volatile anesthetics and lidocaine observed in the present study may be caused partly by a decrease in the hepatic metabolism of lidocaine through a reduction of hepatic blood flow, because hepatic metabolism largely contributes to the clearance of lidocaine (15). However, a synergistic interaction in the depressant effect on the activation time was similarly observed between the volatile anesthetics and procainamide, in spite of the fact that hepatic metabolism of procainamide occurs to a less extent compared to that of lidocaine (15). Therefore, a reduction in hepatic metabolism may not largely contribute to the synergistic interaction. Considering the present results and our previous results that a synergistic interaction was observed between halothane and lidocaine or procainamide (13), it seems that a synergistic interaction may be observed between most volatile anesthetics and the class I antiarrhythmic drugs. Although lidocaine and procainamide are class Ib and Ia antiarrhythmic drugs, respectively, a similar synergistic interaction was observed with the two drugs. Therefore, it seems that a difference in the subtype may not cause any difference in the interaction.

As was demonstrated with halothane and quinidine (12), it is probable that the interaction between volatile anesthetics and lidocaine or procainamide may be attributed to an interaction in the direct electrophysiologic effects of these drugs on the cell membranes of cardiac muscle. As mentioned above, some of the volatile anesthetics and class I antiarrhythmic drugs inhibit sodium channels, although the mechanisms of these drugs may be different. Volatile anesthetics depress cell-to-cell electrical coupling, although the effects of class I antiarrhythmic drugs on cell-to-cell electrical coupling are not clear. The synergistic effect observed in the present study may be caused by the effects of these drugs on sodium channels and cell-to-cell electrical coupling.

Although a further study is required to clarify the mechanism of the interaction between volatile anesthetics and class I antiarrhythmic drugs, an interaction in the direct electrophysiologic effects on cell membranes as well as their pharmacokinetics may contribute to the synergistic interaction. Because of these synergistic interactions, care should be taken so that the dose of class I antiarrhythmic drug may not be an overdose during anesthesia with the volatile anesthetic.

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