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Comparative Efficacy of Antiarrhythmic Agents in Preventing Halothane-Epinephrine Arrhythmias in Rats

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Background: **Because the relative efficacy of antiarrhythmic agents on halothane-epinephrine arrhythmias has not been well characterized, this study was undertaken to comparatively evaluate the antiarrhythmic action of Na^+-, K^+- and Ca^{2+}-channel blockers on epinephrine-induced ventricular arrhythmias during halothane anesthesia in rats.**

Methods: **Rats were anesthetized at random with either halothane (1.5%), isoflurane (2.0%), or pentobarbital (50 mg/kg intraperitoneally), and the lungs were mechanically ventilated with oxygen. The rats were studied in three consecutive protocols. Protocol I determined the arrhythmogenic thresholds of epinephrine during the three types of anesthesia in 33 rats. Protocol II determined the arrhythmogenic thresholds of epinephrine during halothane anesthesia in 64 rats receiving saline (control) or one of five antiarrhythmic agents. Protocol III measured the duration of epinephrine-induced arrhythmias during halothane anesthesia in 42 rats receiving saline (control) or one of five antiarrhythmic agents.**

Results: **In protocol I, the arrhythmogenic doses of epinephrine during halothane, isoflurane, or pentobarbital anesthesia were 1.7 ± 3.2, 11.1 ± 0.6, and 39.0 ± 3.9 μg/kg, respectively, and the corresponding plasma concentrations were 4.3 ± 0.8, 103.7 ± 9.2, and 246.7 ± 28.9 ng/ml, respectively. In protocol II, the arrhythmogenic doses were similar in rats receiving saline and in those receiving lidocaine. The arrhythmogenic doses in rats receiving verapamil, flecainide (Na^+- and K^+- channel blocker), E-4031(K^+- channel blocker), or amiodarone(K^+- channel blocker with Na^+-, Ca^{2+}-, and beta-blocking activity) increased significantly, *i.e.*, 4.2, 4.2, 5.5, and 31.7 times control ($P < 0.01$). In protocol III, lidocaine had no effect on the duration of arrhythmias. Flecainide, E-4031, and verapamil markedly reduced the duration of arrhythmias induced by epinephrine, 8 μg/kg intravenously ($P < 0.01$), whereas only amiodarone markedly reduced the duration of arrhythmias induced by epinephrine, 16 μg/kg intravenously ($P < 0.01$).**

Conclusions: **It was concluded that agents with K^+- channel blocking properties were the most effective in preventing halothane-epinephrine arrhythmias in rats. (Key words: Anesthetics, volatile: halothane. Heart: arrhythmia. Ions: calcium; potassium; sodium. Species: rat. Sympathetic nervous system, catecholamines: epinephrine.)**

IT has been reported that various kinds of antiarrhythmic agents effectively prevent epinephrine-induced ventricular arrhythmias during halothane anesthesia.[1–4] Recently, potassium channel blockers, in addition to sodium and calcium channel blockers, have been reported to effectively treat ventricular arrhythmias resulting from myocardial ischemia,[5,6] and coronary reperfusion,[7,8] in animals and humans. However, the efficacy of potassium channel blockers to prevent halothane-epinephrine arrhythmias has not been well examined, and relative potencies of sodium, potassium, and calcium channel blockers on halothane-epinephrine arrhythmias have not been well characterized. The current study was carried out to comparatively evaluate the antiarrhythmic action of sodium, potassium, and calcium channel blockers on halothane-epinephrine-induced ventricular arrhythmias.

Materials and Methods

This study was conducted under guidelines provided in the Animal Care Committee of Osaka University

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Medical School. One hundred and thirty-nine Sprague-Dawley male rats weighing 350–500 g (mean ± SD 411.2 ± 32.2) were used and were housed in groups of four on a 12:12-h light-dark cycle with food and water *ad libitum*. The rats were anesthetized with 1.5% halothane in 100% oxygen, 2.0% isoflurane in 100% oxygen, or 50 mg/kg intraperitoneal pentobarbital. A different animal was used for each experiment. After tracheostomy, the lungs were mechanically ventilated with a tidal volume of 4–5 ml at 40–60 breaths/min (Metran Compos β-EA, Tokyo, Japan). The respiratory rates were adjusted to maintain Pa_{CO_2} at 35–45 mmHg. Inspired concentrations of halothane and isoflurane were maintained at 1.5% and 2.0%, respectively (Datex Capnomac multiple gas monitor, Helsinki, Finland). Lead II of the electrocardiogram was monitored continuously. Catheters were inserted into a carotid artery for both pressure monitoring and blood sampling, and into a subclavian vein for administration of drugs. Arterial blood pressure was measured with a pressure transducer (Nihon Kohden AP-641G, Tokyo, Japan). Heart rate was counted by heart rate monitoring unit (Nihon Kohden AT-601G, Tokyo, Japan). The electrocardiogram and arterial blood pressure were recorded continuously with a thermal array recorder (Nihon Kohden WS-641G, Tokyo, Japan). A heating lamp was used to maintain rectal temperature at 37.5–38.5° C. Arterial *p*H and oxygen tension were maintained at 7.35–7.45 and more than 250 mmHg, respectively. After completion of preparation, anesthesia was maintained for 30 min to achieve the steady state.

Three series of experiments were performed. First, the arrhythmogenic threshold of epinephrine during halothane, isoflurane, or pentobarbital anesthesia was determined in 33 rats. After achieving an anesthetic steady state, the arrhythmogenic threshold dose of epinephrine was determined. The arrhythmogenic dose (AD) of epinephrine was defined as the smallest dose that produced three or more premature ventricular contractions within 15 s of injection.[9] Modifying the methods of Laster *et al.*,[10] epinephrine was injected at logarithmically spaced doses (0.5, 1.0, 1.41, 2.0, 2.83, 4.0, 5.67, 8.0, *etc.* μg/kg) after an initial dose of 4.0 μg/kg.[9] In the preliminary study, the 4.0-μg/kg dose caused arrhythmias in most of the halothane-anesthetized rats, but not in pentobarbital-anesthetized rats. The 4.0-μg/kg dose served as an indicator of the direction in which to proceed to establish the AD, *i.e.*, higher or lower dose of epinephrine. This method could decrease the number of epinephrine injections necessary to determine AD. A period of 10–30 min was allowed between each injection. When the criterion for AD was satisfied, a 2-ml arterial blood sample was collected to allow measurement of the concentration of plasma epinephrine.

Secondly, the effects of clinically used antiarrhythmic agents on the arrhythmogenic threshold of epinephrine during halothane anesthesia were determined. We used five different antiarrhythmic agents that had been reported to effectively treat ventricular arrhythmias resulting from myocardial ischemia, digitalis, halothane-epinephrine interaction, and coronary reperfusion. Those were as follows; class I antiarrhythmic agents, lidocaine and flecainide; class III antiarrhythmic agents, amiodarone and E-4031; and class IV antiarrhythmic agents, verapamil. Table 1 summarizes the antiarrhythmic agents and their actions.

Sixty-four rats were anesthetized with 1.5% halothane. When a steady state was achieved, we measured the basal hemodynamic data (arterial blood pressure and heart rate), after which an antiarrhythmic agent was infused by constant infusion pump (Terumo STC-502, Tokyo, Japan) over a period of 5 min. The channel blockers, except for amiodarone, were dissolved in 1 ml of water. Amiodarone was dissolved in 90% water/10% ethyl alcohol, a vehicle that had no effects on epinephrine-induced arrhythmias. The doses were as follows; 5.0 mg/kg lidocaine, 3.0 mg/kg flecainide, 5.0 mg/kg amiodarone, 0.2 mg/kg E-4031, and 0.3 mg/kg verapamil. The dose for each antiarrhythmic agent was determined on the basis of its minimal impact on blood pressure, determined in a preliminary study. The selected dose for each drug was the dose that caused an approximately 15% reduction in systolic arterial blood pressure during 5 min of infusion. Control animals received 1 ml of saline over a 5-min period. When the infusion was finished, the AD of epinephrine was determined in the same manner described above.

Table 1. Antiarrhythmic Agents: Site of Action

Antiarrhythmic agents	Blocking Property			
	Sodium Channel	Calcium Channel	Potassium Channel	β-Adrenoceptor
Lidocaine	+	−	−	−
Verapamil	−	+	−	−
Flecainide	+	−	+	−
E-4031	−	−	+	−
Amiodarone	+	+	+	+

Thirdly, the effects of antiarrhythmic agents on the duration of epinephrine-induced arrhythmias during halothane or pentobarbital anesthesia were measured. In rats, epinephrine-induced arrhythmias tend to occur in a single, uninterrupted chain, the duration of which is proportional to the dose of epinephrine.[9] The arrhythmic episodes are characterized by premature ventricular contractions, ventricular tachycardia, bigeminy, and more complex forms of ventricular arrhythmias. Thirty-six rats were anesthetized with halothane and six were anesthetized with pentobarbital. The antiarrhythmic agents were infused in the same manner as described above. After infusion of channel blockers, each rat received injections of increasing doses of epinephrine (8.0 and 16.0 μg/kg), and the duration of arrhythmias was measured. A period of 30 min was allowed between injections.

Analysis of Plasma Concentration (PC) of Epinephrine

For measurement of the plasma concentration of epinephrine, blood samples were put into precooled plastic tubes containing 20 μl 0.2 M EDTA-2Na and 0.2 M $Na_2S_2O_5$, which were then centrifuged at 4,000 rpm for 10 min at 2° C to separate the plasma. For analysis of epinephrine, 1 ml of plasma was acidified by the addition of 0.5 ml of 2.5% perchloric acid to precipitate protein. The samples were stored at −40° C for not longer than 7 days, until analysis. Epinephrine concentration in deprotenized plasma was determined by an automated double-column high-performance liquid chromatography (HPLC) system (model HLC-8030 Catecholamine Analyzer, Tosoh, Tokyo, Japan).[11] This assay system is based on the diphenylethylenediamine condensation reaction, and its limit of sensitivity is 10 pg/ml for epinephrine, with inter- and intraassay variations of less than 3%.

Table 2. Arrhythmogenic Threshold of Epinephrine during Halothane, Isoflurane, or Pentobarbital Anesthesia

		Epinephrine Threshold	
Anesthesia	N	Arrhythmogenic Dose (μg/kg)	Plama Concentration (ng/ml)
Halothane	11	1.70 ± 0.32	4.34 ± 0.76
Isoflurane	11	11.1 ± 0.63*	103.7 ± 9.2*
Pentobarbital	11	39.0 ± 3.9†	246.7 ± 28.9†

Values are mean ± SEM.

* $P < 0.01$ compared with halothane value.

† $P < 0.01$ compared with halothane or isoflurane value.

Table 3. The Effect of Antiarrhythmic Agents on Arrhythmogenic Threshold of Epinephrine during Halothane Anesthesia

		Epinephrine Threshold		
Treatment	N	Arrhythmogenic Dose (μg/kg)	Log_{10} (Arrhythmogenic Dose) (μg/kg)	Plasma Concentration (ng/ml)
Saline	11	1.50 ± 0.26	0.123 ± 0.06	3.70 ± 0.68
Lidocaine	10	1.77 ± 0.23	0.211 ± 0.06	4.85 ± 0.64
Flecainide	11	6.27 ± 0.53	0.780 ± 0.04†	31.7 ± 6.10
Amiodarone	11	47.5 ± 5.30*	1.642 ± 0.06*	458 ± 81.5*
E-4031	11	8.26 ± 0.66	0.903 ± 0.04†	80.2 ± 11.1
Verapamil	10	6.26 ± 0.79	0.768 ± 0.05†	29.4 ± 4.40

Values are mean ± SEM.

* $P < 0.01$ compared with saline, lidocaine, flecainide, E-4031, or verapamil value.

† $P < 0.01$ compared with saline or lidocaine value.

Statistical Analysis

The data were expressed as means ± SEM. Statistical significance of data, before and after logarithmic conversion, was analyzed by one-way ANOVA, and repeated measures ANOVA followed by Scheffe multiple comparison procedure. Logarithmic conversion of data was performed because of the logarithmic spaced dose regimen (*i.e.*, the conversion produced a more normal distribution of values). Values of $P < 0.05$ were considered significant.

Results

The arrhythmogenic dose (AD) and plasma concentration (PC) values of epinephrine during anesthesia with halothane, isoflurane, or pentobarbital are shown in table 2. The AD of epinephrine during isoflurane and pentobarbital anesthesia were 6.6 and 23 times greater than that during halothane anesthesia, respectively ($P < 0.01$). The PC of epinephrine during isoflurane and pentobarbital anesthesia were 23.9 and 56.9 times greater than that during halothane anesthesia, respectively ($P < 0.01$). Table 3 shows the efficacy of antiarrhythmic agents on the AD and PC of epinephrine during halothane anesthesia. The AD of epinephrine after infusion of lidocaine, flecainide, amiodarone, E-4031, or verapamil were 1.2, 4.2, 31.7, 5.5, and 4.2 times greater than that after saline. The

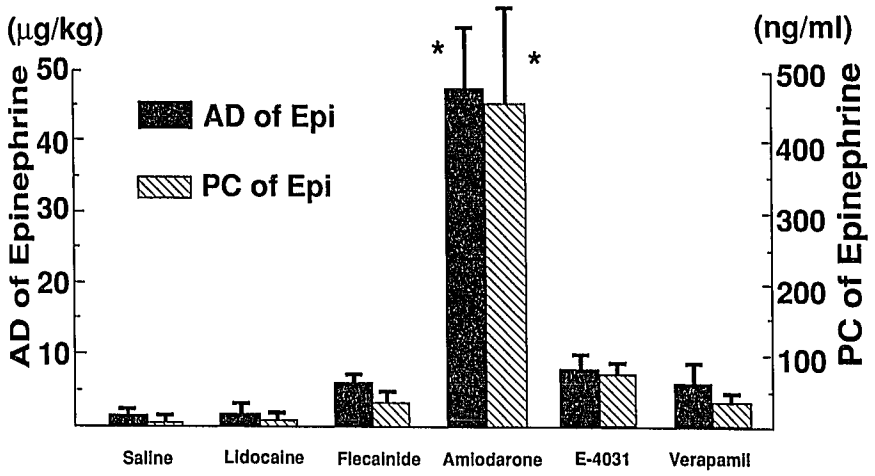

Fig. 1. The effect of antiarrhythmic agents on arrhythmogenic dose (AD) and plasma concentration (PC) of epinephrine during halothane anesthesia. *$P < 0.01$ compared with saline, lidocaine, flecainide, E-4031, or verapamil value.

AD and PC of epinephrine after amiodarone infusion were significantly greater than that after infusion of any other drugs ($P < 0.01$). After logarithmic conversion of data, the AD of epinephrine after flecainide, E-4031, or verapamil infusion was significantly greater than that after saline or lidocaine infusion ($P < 0.01$, figs. 1 and 2). Systolic or diastolic arterial pressure at the time of arrhythmias after flecainide, amiodarone ($P < 0.01$), or E-4031 ($P < 0.05$) infusion was significantly greater than that after saline, but that after verapamil infusion was similar to that after saline. The greater arterial pressure seen after amiodarone, flecainide, and E-4031 was caused by a better maintenance of sinus rhythm. Systolic arterial pressure during infusion of lidocaine, flecainide, E-4031 ($P < 0.05$), or verapamil ($P < 0.01$) was significantly lower than that of basal state, but within the intended 15% limit. Heart rate was significantly decreased only by flecainide ($P < 0.01$), but not by other compounds (table 4). Table 5 shows the efficacy of antiarrhythmic agents on the duration of epinephrine-induced arrhythmias during halothane anesthesia. Amiodarone, E-4031, flecainide, and verapamil markedly reduced the duration of arrhythmias induced by 8.0 μg/kg epinephrine during halothane anesthesia to a degree similar to that during pentobarbital anesthesia ($P < 0.01$). However, only amiodarone reduced

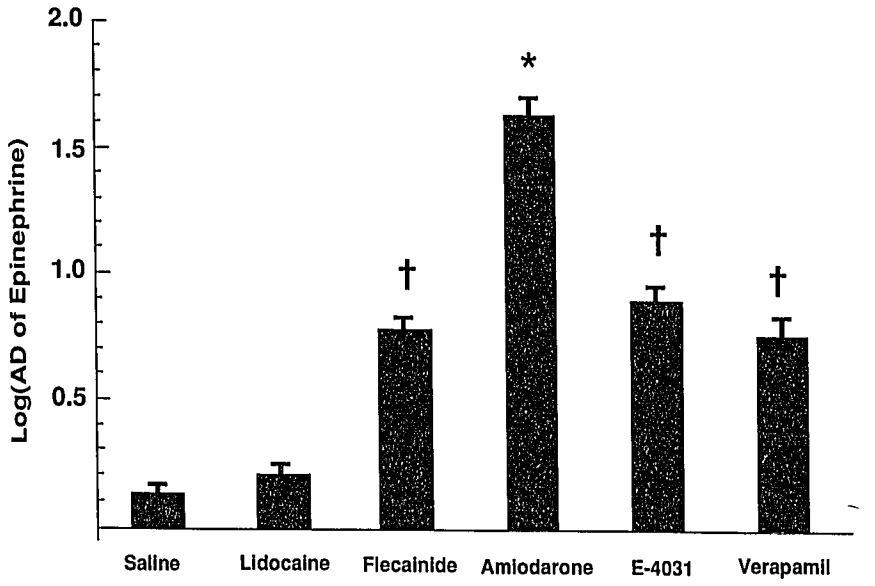

Fig. 2. The effect of antiarrhythmic agents on arrhythmogenic dose (AD) of epinephrine after logarithmic conversion during halothane anesthesia. *$P < 0.01$ compared with saline, lidocaine, flecainide, E-4031, or verapamil value; †$P < 0.01$ compared with saline or lidocaine value.

Table 4. The Effect of Antiarrhythmic Agents on Blood Pressure and Heart Rate before Antiarrhythmic Agent Infusion (Basal), before Epinephrine Injection (Infusion), and at the Time of Arrhythmias (Epinephrine)

Treatment	SAP (mmHg)			DAP (mmHg)			HR (beats/min)		
	Basal	Infusion	Epinephrine	Basal	Infusion	Epinephrine	Basal	Infusion	Epinephrine
Saline	100.6 ± 4.1	100.0 ± 4.1	148.6 ± 2.5	71.3 ± 4.8	71.0 ± 4.1	107.6 ± 3.5	318.1 ± 13	318.0 ± 12	381.3 ± 11
Lidocaine	101.4 ± 2.8	88.4 ± 4.0§	147.0 ± 3.6	75.6 ± 4.5	61.0 ± 4.5§	112.3 ± 3.5	324.6 ± 9.7	307.8 ± 10	364.6 ± 13
Flecainide	102.1 ± 6.2	88.5 ± 5.1§	174.9 ± 5.6*	68.4 ± 4.8	55.0 ± 3.8	130.3 ± 4.2*	291.3 ± 9.3	254.5 ± 9.1‡	362.4 ± 11
Amiodarone	106.1 ± 3.8	97.5 ± 4.8	200.7 ± 4.0*	77.3 ± 3.6	65.4 ± 4.5§	152.3 ± 4.2*	310.7 ± 9.0	300.9 ± 6.2	336.7 ± 12
E-4031	104.5 ± 5.7	93.5 ± 4.8§	171.2 ± 5.1†	76.2 ± 4.5	65.0 ± 4.2§	131.0 ± 3.8*	320.5 ± 6.8	291.8 ± 6.6	355.4 ± 13
Verapamil	102.7 ± 4.6	84.5 ± 4.0‡	169.0 ± 3.8	76.5 ± 2.8	59.6 ± 3.1‡	125.4 ± 3.9	326.3 ± 7.1	306.4 ± 11	353.2 ± 12

SAP = systolic arterial pressure; DAP = diastolic arterial pressure; HR = heart rate.
Values are mean ± SEM.
* $P < 0.01$ compared with saline value.
† $P < 0.05$ compared with saline value.
‡ $P < 0.01$ compared with basal value.
§ $P < 0.05$ compared with basal value.

the duration of arrhythmias induced by 16.0 μg/kg epinephrine ($P < 0.01$). Lidocaine had no effect on the duration of arrhythmias induced by epinephrine, either 8.0 or 16.0 μg/kg (table 5).

Discussion

Although the mechanism for halothane-epinephrine-induced ventricular arrhythmias has been suggested to involve triggered activity, reentry is also considered to be a possible mechanism.[12] Halothane can depress intraventricular conduction velocity,[13,14] and this effect is potentiated by α_1-adrenergic activity.[15] Epinephrine exerts its actions through α_1- and β-adrenergic receptors.[16] α_1- and β-adrenergic stimulation affect the refractory period oppositely;[17,18] that is, the former prolongs the refractoriness, and the latter shortens it. These converse actions may cause large differences in recovery time in various areas of myocardium, facilitating unidirectional block. Thus, the combination of halothane and epinephrine can provoke arrhythmias with a reentry mechanism.[12] Although both α_1- and β-adrenergic stimulations induce the influx of extracellular calcium through the independent receptor effector mechanisms,[17] and the triggered activity following delayed afterdepolarization is a typical example of arrhythmia induced by intracellular calcium elevation,[19] halothane was shown to inhibit slow channel calcium fluxes.[20] Furthermore, oubaine-induced arrhythmia, a typical example of triggered activity,[19] was attenuated by halothane inhalation.[21,22] Thus, this mechanism does not seem to be involved in the mechanism of halothane-epinephrine arrhythmias. Hemodynamic parameters, especially systolic arterial pressure and atrial rhythm, have been regarded to play an important role in the genesis of halothane-epinephrine arrhythmias.[23] In the current study, the systolic arterial pressures in the flecainide, E-4031, and amiodarone groups was higher than that of control, and sinus rhythm was better maintained in these groups. These results indicate that the drugs with potassium channel blocking properties can inhibit epinephrine-induced arrhythmias, even if the blood pressure was increased to a threshold level, and that the antiarrhythmic effect of these compounds could not be caused by cardiodepression.

The principal findings in the current study are that amiodarone is the most effective for treatment of the halothane-epinephrine arrhythmias, and that the agents with potassium channel blocking properties, *i.e.*, E-4031 and flecainide, are as effective as a calcium chan-

Table 5. The Duration of Epinephrine-induced Arrhythmia during Halothane or Pentobarbital Anesthesia in the Presence or Absence of Antiarrhythmic Agents

Anesthesia	Treatment	N	Duration of Epinephrine Arrhythmia (s)	
			8.0 μg/kg Epinephrine	16.0 μg/kg Epinephrine
Halothane	Saline	6	32.2 ± 0.79	59.2 ± 1.5
	Lidocaine	6	28.2 ± 2.9	56.8 ± 4.0
	Flecainide	6	2.33 ± 1.1*	44.8 ± 1.8
	Amiodarone	6	0*	2.2 ± 1.2†
	E-4031	6	3.8 ± 1.2*	26.0 ± 2.4†‡
	Verapamil	6	0*	18.0 ± 4.5†§
Pentobarbital	Saline	6	0*	4.5 ± 1.5†

Values are mean ± SEM.

* $P < 0.01$ compared with saline or lidocaine value.

† $P < 0.01$ compared with saline, lidocaine, or flecainide value.

‡ $P < 0.01$ compared with amiodarone or pentobarbital value.

§ $P < 0.05$ compared with amiodarone value.

nel blocker (verapamil), and more effective than a sodium channel blocker (lidacaine).

Lidocaine, one of the most popular sodium channel blockers, has been known to be a class I antiarrhythmic agent. However, in the dose used, it had no efficacy on the epinephrine-induced ventricular arrhythmias and the duration of arrhythmias.

Verapamil has already been shown to prevent halothane-epinephrine arrhythmias in dogs.[4] Our study has confirmed this previous finding. Although calcium is recognized to play an important role in the genesis of several types of arrhythmias,[24] the role of calcium in the genesis of halothane-epinephrine arrhythmias has not been well understood. Epinephrine induces intracellular calcium elevation, producing various physiologic effects. Thus, the calcium channel blocking may attenuate these actions, including arrhythmic property.

E-4031 is a recently developed class III antiarrhythmic agent,[5,6] and is considered to be a pure potassium channel blocker that can inhibit only delayed rectifier current.[25] Heretofore, the role of potassium channels in the halothane-epinephrine arrhythmias has not been well explored. In the current study, E-4031 prevented the epinephrine-induced arrhythmias during halothane anesthesia more potently than did a sodium channel blocker, lidocaine, and as effectively as a calcium channel blocker, verapamil. The delayed rectifier current is known to play an important role in the repolarizing process,[26] and the blocking of this current produces prolongation of refractory period.[27] Because the reentry has been considered to be a probable mechanism for halothane-epinephrine arrhythmias,[12] one may deduce that this action may prevent the genesis of reentry circuit facilitated by the combination of halothane and epinephrine, inhibiting the occurrence of the arrhythmias.

Although flecainide, similar to lidocaine, is considered to be a sodium channel blocker and a class I antiarrhythmic drug, its antiarrhythmic effect was significantly greater than that of lidocaine and the same as that of verapamil and E-4031. It should be noted, however, that lidocaine is considered a class IA blocker, but flecainide is considered a class IC blocker that blocks the activated state of the sodium channel. This latter effect is somewhat different than that of lidocaine, which is less potent. Furthermore, it has been reported that flecainide is able to exert potassium channel blocking property and can inhibit delayed rectifier current at a clinically relevant concentration.[25] Thus, the responsible channel involved in its antiarrhythmic effect may be potassium channels, but not sodium channels.

Among the agents tested, amiodarone is the most effective in preventing halothane-epinephrine arrhythmias. Although amiodarone is classified as a class III antiarrhythmic agent,[26] and is effective in blocking potassium channels, it can also block both sodium[28] and calcium channels.[29] In addition, intravenous amiodarone exerts noncompetitive β_1-adrenergic antagonist activity.[30–32] Therefore, this agent can inhibit the genesis of halothane-epinephrine arrhythmias almost maximally, because β_1-adrenergic blockers have been shown to prevent the arrhythmias.[33]

It is difficult to compare different kinds of cation channel blockers in terms of their equipotency. Thus, we determined the doses of the cation channel blockers on the basis of a minimal impact on the blood pressure, *i.e.*, the dose that caused an approximately 15% reduction in systolic arterial pressure during 5 min of infusion. In this study, the reduction in systolic arterial blood pressure was actually within 15%. The doses adopted are approximately three to five times greater than the clinical dosage, except for amiodarone. The clinical dosage of amiodarone is 5–10 mg/kg.[8] Thus, the efficacy of amiodarone in preventing arrhythmias is even more remarkable considering its usage in clinically relevant doses, *versus* the much higher doses used for the other agents.

The efficacy of lidocaine, one of the most popular sodium channel blockers, for treating epinephrine-induced arrhythmias during halothane anesthesia has been shown in a clinical trial.[34] However, we could not demonstrate that lidocaine significantly exerts an antiarrhythmic property using the present paradigm. Although the reason for this discrepancy is not clear, the difference in method of epinephrine administration may be involved. In the previous clinical study, epinephrine was administered subcutaneously for hemostasis. In comparison, epinephrine was administered intravenously as a bolus in the current study. The arrhythmogenic action of intravenously administered epinephrine may require lidocaine doses greater than those used in this study. Some reports showed that a massive dose of lidocaine was required to prevent intravenous epinephrine-induced arrhythmias with halothane in dogs.[1,35] In addition, a species difference may be involved in the vulnerability to myocardial sensitization by halothane.

Our results, shown in table 2, indicate that we could produce typical halothane epinephrine arrhythmias in rats. Laster *et al.* examined the AD of epinephrine during halothane anesthesia in rats using a similar paradigm and reported that the mean AD was 2.4 μg/kg.[10] This result is similar to ours. However, Miletich *et al.*[36] and Mayer *et al.*[9] reported that the AD was 9.7 and 10.9 μg/kg, respectively. Their method and criterium for the arrhythmogenic threshold are similar to ours. Although the reason for this discrepancy is obscure, the difference in age of rats tested may explain, in part, the difference of the results. In fact, the vulnerability to myocardial sensitization by halothane is different between adults and children.[37] Clearly, additional studies are required to elucidate the difference.

It is possible that there is a species difference in the AD of epinephrine. Sumikawa *et al.*[38] and Hayashi *et al.*[39] reported that the AD and PC of epinephrine in dogs were 4.18 μg/kg and 38.7 ng/ml for halothane, 19.6 μg/kg and 207.3 ng/ml for isoflurane, and 34.7 μg/kg and 296.5 ng/ml for pentobarbital, respectively. These thresholds seem to be higher than those in rats. In addition to the species difference, the different thresholds may be caused, in part, by the different epinephrine dosing regimen, *i.e.*, in rats, epinephrine was injected by bolus, but in dogs, it was infused for over 3 min.

In conclusion, agents with potassium channel blocking properties were the most effective in preventing halothane-epinephrine arrhythmias in rats. This indicates that further studies of the role of potassium channels in halothane-epinephrine arrhythmias are needed.

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