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Halothane sensitizes the canine heart to pharmacological I_{Kr} blockade

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Abstract

The effects of halothane and pentobarbital on the cardiovascular system were compared using the in vivo canine models. The ventricular repolarization process was longer under the halothane-anesthesia than pentobarbital-anesthesia. Intravenous administration of a selective blocker of rapidly activating delayed rectifier K^+ currents (I_{Kr}) sematilide prolonged the ventricular repolarization period without affecting the intraventricular conduction under both anesthesia; however, the potency was about 1.5-folds greater under the halothane-anesthesia than pentobarbital-anesthesia. These results suggest that halothane can more effectively sensitize the heart to pharmacological I_{Kr} blockade, resulting in the excessive QT interval prolongation. Thus, the halothane-anesthetized canine model can be useful for predicting the in vivo I_{Kr} blocking property of new drugs.

Keywords: Halothane; Pentobarbital; Sematilide; Ventricular repolarization

1. Introduction

In the field of safety pharmacology, drug-induced QT interval prolongation is currently a hot topic of concern, since excessive QT interval prolongation may induce lethal ventricular arrhythmias; namely, torsades de pointes. Thus, the regulatory authorities require pharmaceutical companies to carefully examine effects of newly synthesized drugs on HERG (human ether-á-gogo related gene) channels, encoding the pore-forming subunit of rapidly activating delayed rectifier K^+ currents (I_{Kr}) of the heart. Also, for estimating drug-induced QT prolongation, use of in vivo models is strongly recommended in the draft guideline ICH S7B for safety pharmacology studies (The ICH Steering Committee, 2004). Among in vivo models, anesthetized animal models have been shown to be more sensitive in predicting the potential of the drug to prolong the QT interval than non-anesthetized models (The ICH Steering Committee, 2004).

While various types of anesthetics have been used for animal studies in evaluating cardiovascular profiles of drugs, the extent of QT interval prolongation by several I_{Kr} blockers in the halothane-anesthetized dogs has been shown to be similar to that observed in the clinical phase I studies (Satoh et al., in press). On the other hand, in vitro electrophysiological studies have shown that some anesthetics including halothane and pentobarbital can significantly suppress the HERG channels (Bachmann et al., 2002; Li and Correa, 2002). Therefore, the QT interval-prolonging action of drugs in vivo may be affected by the anesthetic used.

The present study was designed to compare the effects of halothane and pentobarbital on the cardiovascular system. For this purpose, we initially compared the basal cardiovascular variables under the halothane- and pentobarbital-anesthesia using an animal group of 5 dogs. Next, we compared the influence of halothane and pentobarbital on cardiovascular response to pharmacological I_{Kr} blockade by sematilide (Beatch et al., 1996; Ishii et al., 1997).

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2. Methods

Experiments were carried out using beagle dogs of either sex weighing approximately 10 kg. Animals were obtained through the Animal Laboratory for Research of University of Yamanashi. All experiments were performed according to Guidelines for Animal Experiments, University of Yamanashi.

2.1. Induction and maintenance of anesthesia

The animals were anesthetized with either halothane or pentobarbital.

Halothane-anesthesia: Thiopental sodium (30 mg/kg, i.v.) was initially administered. After intubation with a cuffed endotracheal tube, 1.0% halothane vaporized with 100% oxygen was inhaled using a volume-limited ventilator (SN-480-3, Shinano, Tokyo, Japan). Tidal volume and respiratory rate of the ventilator were set at 20 ml/kg and 15 strokes/min, respectively (Sugiyama et al., 2003; Takahara et al., 2003).

Pentobarbital-anesthesia: Pentobarbital sodium (30 mg/kg, i.v.) was administered, which was supplemented at a rate of 5 mg/kg/h, as previously described (Takahara et al., 1990). After intubation with a cuffed endotracheal tube, the dogs were ventilated with 100% oxygen using a volume-limited ventilator (SN-480-3, Shinano). Tidal volume and respiratory rate of the ventilator were set at 20 ml/kg and 15 strokes/min, respectively.

2.2. Measurement of cardiohemodynamic parameters

A heparinized catheter was inserted through the right femoral artery for continuous monitoring of the systemic blood pressure. To prevent blood clotting, heparin calcium (100 IU/kg) was intravenously administered. A thermodilution catheter (TC-704, Nihon Kohden, Tokyo, Japan) was positioned at the right side of the heart via the right femoral vein, and the cardiac output was measured by a standard thermodilution method using a cardiac output computer (MFC-1100, Nihon Kohden). Total peripheral resistance was calculated using the basic equation: mean blood pressure/cardiac output. A pig-tail catheter was positioned at the left ventricle through the right femoral artery to measure the left ventricular pressure. The maximum upstroke velocity of the left ventricular pressure and the left ventricular end-diastolic pressure were obtained during the sinus rhythm to estimate the contractility and the preload to the left ventricle, respectively.

2.3. Measurement of electrophysiological parameters

The surface lead II electrocardiogram (ECG) was obtained from the limb electrodes. Corrected QT intervals were calculated with the formulas by Bazett (QTc (B)) and Van de Water (QTc (V)) (Bazett, 1920; Van de Water et al., 1989). A quad-polar electrodes catheter was positioned at the non-coronary cusp of the aortic valve through the left femoral artery to obtain the His bundle electrogram. A bi-directional steerable monophasic action potential (MAP) recording/pacing combination catheter (1675P, EP Technologies Sunnyvale, CA, USA) was positioned at the endocardium of the interventricular septum in the right ventricle through the left femoral vein to obtain MAP signals. The signals were amplified with a DC preamplifier (300, EP Technologies). The duration of the MAP signals was measured as an interval, along a line horizontal to the diastolic baseline, from the MAP upstroke to the desired repolarization level, and the interval (ms) at 90% repolarization was defined as MAP_{90}.

The heart was electrically driven using a cardiac stimulator (SEC-3102, Nihon Kohden) with the MAP recording/pacing combination catheter placed in the right ventricle. The stimulation pulses were rectangular in shape, 1–2 V (about twice the threshold voltage) and of 1 ms duration. MAP_{90} was measured during the sinus rhythm ($MAP_{90(sinus)}$) and at a pacing cycle length of 400 ms ($MAP_{90(CL400)}$) and 300 ms ($MAP_{90(CL300)}$). The effective refractory period was assessed by the programmed electrical stimulation to the right ventricle. The pacing protocol consisted of five beats of basal stimuli in a cycle length of 400 ms followed by an extra stimulus of various coupling intervals. Starting in the late diastole, the coupling interval was shortened in 5- to 10-ms decrements until refractoriness occurred. The duration of the terminal repolarization phase of the ventricle was calculated by the difference between the $MAP_{90(CL400)}$ and effective refractory period at the same site, which is the electrically vulnerable period of the ventricular muscle (Sugiyama and Hashimoto, 2002).

2.4. Experimental protocol

2.4.1. Experiment 1: comparison of basal cardiovascular variables under halothane-anesthesia and pentobarbital-anesthesia

Five dogs were anesthetized with halothane followed by pentobarbital with an interval of >1 month. Cardiohemodynamic and electrophysiological parameters were continuously monitored using a polygraph system (RM-6000, Nihon Kohden), and analyzed using a real time full automatic data analysis system (MP/VAS 3 for Macintosh ver 1.0, Physio-Tech, Tokyo, Japan). Each measurement of the ECG, MAP, and His bundle electrogram was the mean of three consecutive recordings. The cardiovascular variables were assessed in the following order. The cardiac output was measured twice. Next, the ECG, His bundle electrogram, systemic and left ventricular pressure and MAP signals were recorded under the sinus rhythm. Then, the MAP signals were recorded at a pacing cycle length of 400 and 300 ms. Finally, the effective refractory

period was assessed with the programmed electrical stimulation as described above.

2.4.2. Experiment 2: comparison of the influence of halothane and pentobarbital on cardiovascular response to sematilide

The dogs were anesthetized with either halothane (n=4) or pentobarbital (n=4). After the basal cardiohemodynamic and electrophysiological assessments using the same protocol, as described in the experiment 1, sematilide in a low dose of 0.03 mg/kg was administered over 10 min. Each variable was assessed 5, 10, 15, 20 and 30 min after the start of the infusion. Next, sematilide in a middle dose of 0.3 mg/kg was additionally administered over 10 min and each variable was observed in the same manner. Finally, sematilide in a high dose of 3 mg/kg was administered over 10 min and each variable was observed 5, 10, 15, 20, 30, 45 and 60 min after the start of the infusion.

2.5. Drugs

Sematilide (*N*-[2(diethylamino)ethyl]-4-[(methylsulfonyl)amino]-benzamide hydrochrolide; MW=349.88) was provided from Nippon Roussel (Tokyo, Japan), which was dissolved in saline. The following drugs were also purchased: pentobarbital sodium (Tokyo Kasei, Tokyo, Japan), thiopental sodium (Tanabe Seiyaku, Osaka, Japan), halothane (Takeda Chemical Industries, Tokyo, Japan) and heparin calcium (Mitsui Pharmaceuticals, Tokyo, Japan).

2.6. Statistical analysis

Data are expressed as the mean±S.E.M. The statistical significances of the differences within a parameter were evaluated by paired Student t-test or one-way, repeated-measures analysis of variance (ANOVA) followed by Contrast for mean values comparison. A P value <0.05 was considered statistically significant.

3. Results

3.1. Experiment 1: comparison of cardiovascular variables under the halothane-anesthesia and pentobarbital-anesthesia

Table 1 summarizes the results of cardiovascular variables under the halothane- or pentobarbital-anesthesia (n=5 for each anesthesia). The heart rate, mean blood pressure, maximum upstroke velocity of the left ventricular pressure, and cardiac output under the halothane-anesthesia were significantly lower than those under the pentobarbital-anesthesia, whereas the left ventricular end-diastolic pressure under the halothane anesthesia was significantly higher than that under the pentobarbital anesthesia. No significant change was detected in any of the ECG parameters. The $MAP_{90(sinus)}$, $MAP_{90(CL400)}$, $MAP_{90(CL300)}$, effective refractory period and terminal repolarization period under the halothane-anesthesia were longer than those under the pentobarbital-anesthesia, whereas no significant difference was detected in the atrio-His or His-ventricular interval.

Table 1
Comparison of cardiovascular variables under the halothane-anesthesia and pentobarbital-anesthesia using an animal group of five dogs

		Halothane	Pentobarbital	
HR	beats/min	118±10	154±9	P<0.05
MBP	mm Hg	114±4	143±4	P<0.05
$LVdP/dt_{max}$	mm Hg/s	2329±205	4499±328	P<0.05
LVEDP	mm Hg	11±1	4±1	P<0.05
CO	L/min	1.66±0.08	2.67±0.29	P<0.05
TPR	mm Hg/min/L	71.6±2.4	56.6±5.5	P<0.05
PR	ms	106±3	96±4	
QRS	ms	69±2	64±3	
QT	ms	263±10	238±5	
QTc (V)	ms	309±12	288±3	
QTc (B)	ms	374±22	375±6	
AH	ms	83±3	72±4	
HV	ms	28±3	27±1	
$MAP_{90(sinus)}$	ms	231±5	192±10	P<0.05
$MAP_{90(CL400)}$	ms	236±4	192±7	P<0.05
$MAP_{90(CL300)}$	ms	218±5	180±6	P<0.05
ERP	ms	205±5	178±6	P<0.05
TRP	ms	31±5	14±2	P<0.05

Data are expressed as mean±S.E.M. HR, heart rate; MBP, mean blood pressure; $LVdP/dt_{max}$, maximum upstroke velocity of the left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; CO, cardiac output; TPR, total peripheral vascular resistance; PR, PR interval; QRS, QRS width; QT, QT interval; QTc (V), QT interval corrected by Van de Water's formula; QTc (B), QT interval corrected by Bazett's formula; AH, atrio-His interval; HV, His-ventricular interval; $MAP_{90(sinus)}$, duration of monophasic action potential at a level of 90% repolarization (MAP_{90}) during the sinus rhythm; $MAP_{90(CL400)}$, MAP_{90} at a fixed basic cycle length of 400 ms; $MAP_{90(CL300)}$, MAP_{90} at a fixed basic cycle length of 300 ms; ERP, effective refractory period; TRP, terminal repolarization period.

3.2. Experiment 2: comparison of the influence of halothane and pentobarbital on cardiovascular response to sematilide

3.2.1. Effects on the blood pressure and heart rate

The time courses of changes in the heart rate and mean blood pressure are summarized in Fig. 1. In the halothane-anesthetized animal group (n=4), the pre-drug control values of the heart rate and mean blood pressure were 122±10 beats/min and 132±1 mm Hg, respectively. After the low dose of 0.03 mg/kg as well as the middle dose of 0.3 mg/kg of sematilide infusion, no significant change was detected in the heart rate or mean blood pressure. After the high dose of 3 mg/kg, the heart rate decreased for 45–60 min, whereas no significant change was detected in the mean blood pressure.

In the pentobarbital-anesthetized animal group (n=4), the pre-drug control values of the heart rate and mean blood pressure were 153±9 beats/min and 145±3 mm Hg, respectively. After the low dose, the heart rate decreased

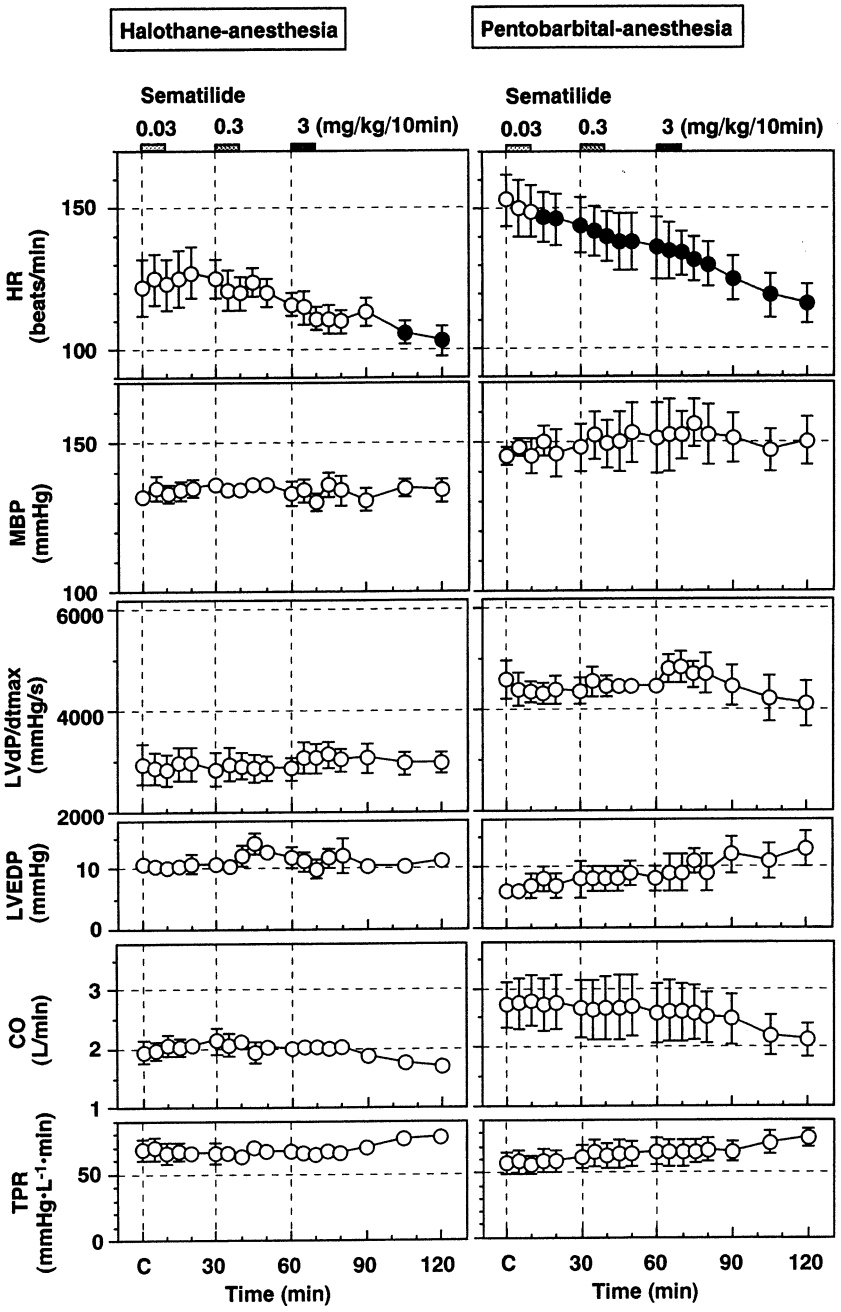

Fig. 1. Time courses of the heart rate (HR), mean blood pressure (MBP), maximum upstroke velocity of left ventricular pressure ($LVdP/dt_{max}$), left ventricular end-diastolic pressure (LVEDP), cardiac output (CO) and total peripheral vascular resistance (TPR). The cardiohemodynamic effects of sematilide under the halothane anesthesia (n=4) are shown in the left panel, while those under the pentobarbital anesthesia (n=4) are depicted in the right panel. Data are presented as mean±S.E.M. The closed symbols represent the significant differences from each control (C) value by $P<0.05$.

for 15–30 min. After the middle dose, the heart rate decreased for 5–30 min. After the high dose, the heart rate decreased for 5–60 min. No significant change was detected in the mean blood pressure.

3.2.2. Effects on the maximum upstroke velocity of the left ventricular pressure, left ventricular end-diastolic pressure, cardiac output and total peripheral vascular resistance

The time courses of changes in the maximum upstroke velocity of the left ventricular pressure, left ventricular end-diastolic pressure, cardiac output and total peripheral vascular resistance are summarized in Fig. 1. In the halothane group (n=4), the pre-drug control values of these variables were 2932±402 mm Hg/s, 11±1 mm Hg, 1.95±0.19 l/min and 68.2±7.8 mm Hg/min/l, respectively. In the pentobarbital group (n=4), the pre-drug control values were 4604±383 mm Hg/s, 6±1 mm Hg, 2.71±0.39 l/min and 57.5±7.7 mm Hg/min/l, respectively. No significant change was detected in any of these variables after the sematilide administration in the respective groups.

3.2.3. Effects on the ECG parameters

Typical tracings of the effects of sematilide on ECG are depicted in Fig. 2, and the time courses of changes in the ECG parameters are summarized in Fig. 3. In the halothane group (n=4), the pre-drug control values of the PR interval, QRS width, QT interval, QTc (V) and QTc (B) were 104±5, 63±5, 276±14, 323±11 and 396±11 ms, respectively. After the low dose, no significant change was detected in these ECG parameters. After the middle dose, the QT interval, QTc (V) and QTc (B) were prolonged for 10–30 min, for 15–30 min and for 15–30 min, respectively. After the high dose, the QT interval, QTc (V) and QTc (B) were prolonged for 5–60 min. No significant change was detected in the PR interval or QRS width.

In the pentobarbital group (n=4), the pre-drug control values of the PR interval, QRS width, QT interval, QTc (V) and QTc (B) were 93±4, 69±1, 238±5, 288±2 and 375±6 ms, respectively. After the low dose, no significant change was detected in the ECG parameters. After the middle dose, only the QT interval was prolonged for 10–30 min. Meanwhile, no significant change was detected in the other parameters. After the high dose, the QT interval and QTc (V) were prolonged for 5–60 min. No significant change was detected in the PR interval, QRS width or QTc (B).

3.2.4. Effects on the His bundle electrogram and MAP signals during the sinus rhythm

Typical tracings of the effects of sematilide on the His bundle electrogram and MAP signals are depicted in Fig. 2, and thetime courses of changes in the atrio-His and His-ventricular intervals and $MAP_{90(sinus)}$ during sinus rhythm are summarized in Fig. 3. In the halothane group (n=4), the pre-drug control values of the atrio-His and His-ventricular intervals and $MAP_{90(sinus)}$ were 76±3, 30±1 and 231±16 ms, respectively. After the low dose, no significant change was detected in the $MAP_{90(sinus)}$. After the middle dose, the $MAP_{90(sinus)}$ was prolonged at 10 and 30 min. After the high dose, the $MAP_{90(sinus)}$ was prolonged for 5–60 min. No significant change was detected in the atrio-His or His-ventricular interval.

In the pentobarbital group (n=4), the pre-drug control values of the atrio-His and His-ventricular intervals and $MAP_{90(sinus)}$ were 70±4, 28±1 and 192±9 ms, respectively. After the low dose as well as the middle dose, no significant change was detected in the $MAP_{90(sinus)}$. After the high dose, the $MAP_{90(sinus)}$ was prolonged for 15–60 min. No significant change was detected in the atrio-His or His-ventricular interval.

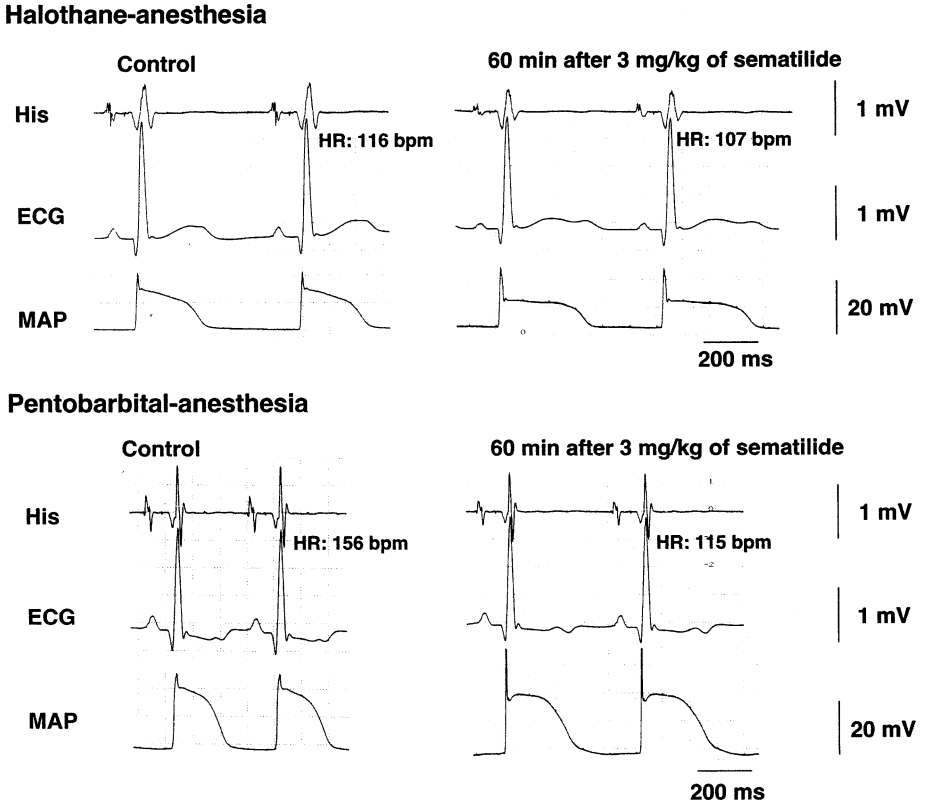

Fig. 2. Typical tracings of His bundle electrogram (His), surface lead II electrocardiogram (ECG) and monophasic action potentials (MAP) recorded from the right ventricle during the sinus rhythm before (Control) and 60 min after the start of 3 mg/kg of sematilide administration. The tracings under the halothane anesthesia are shown in the upper panel, whereas those under the pentobarbital anesthesia are depicted in the lower panel.

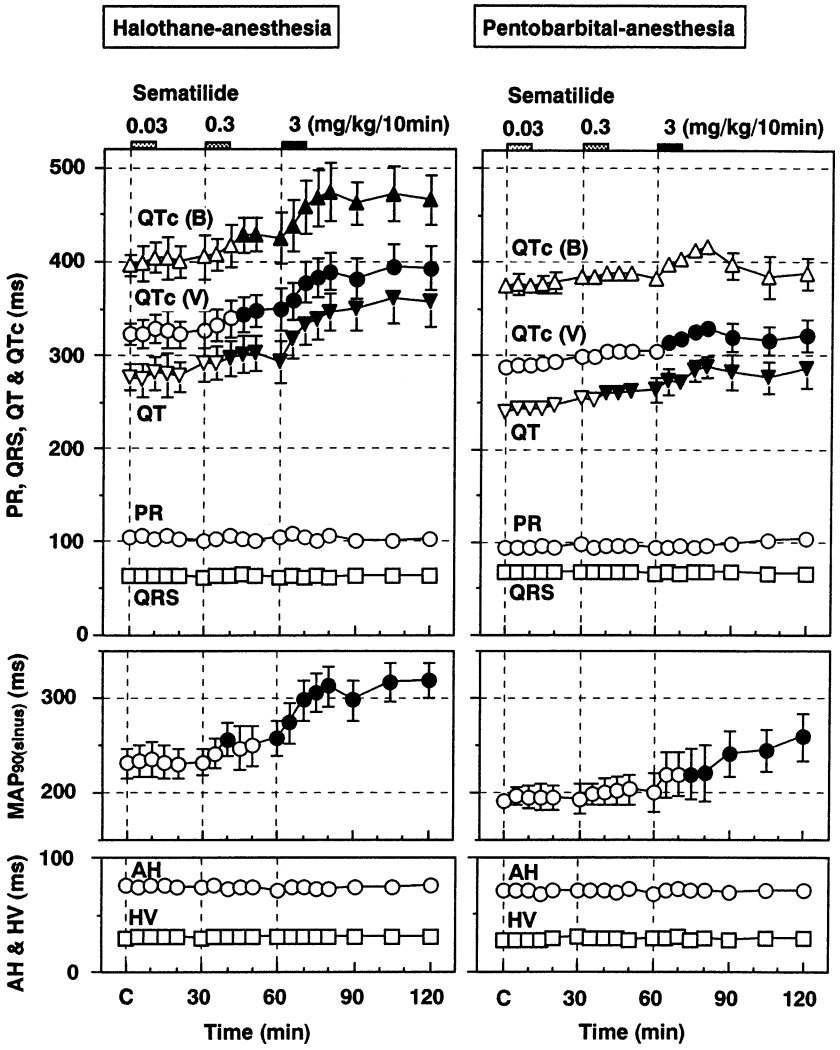

Fig. 3. Time courses of the PR interval (circles), QRS width (squares) and QT interval (triangles), QTc (B) (triangles: corrected by Bazett's formula), QTc (V) (circles: corrected by Van de Water's formula), duration of monophasic action potential at a level of 90% repolarization (MAP_{90}) during the sinus rhythm ($MAP_{90(sinus)}$, circles), atrio-His interval (AH, circles) and His-ventricular interval (HV, squares). The electrophysiological effects of sematilide under the halothane anesthesia (n=4) are shown in the left panel, while those under the pentobarbital anesthesia (n=4) are depicted in the right panel. Data are presented as mean±S.E.M. The closed symbols represent the significant differences from each control (C) value by $P<0.05$.

3.2.5. Effects on the monophasic action potential, effective refractory period and terminal repolarization period at a fixed ventricular pacing rate

The time courses of changes in the $MAP_{90(CL400)}$, $MAP_{90(CL300)}$, effective refractory period and terminal repolarization period are summarized in Fig. 4. In the halothane group (n=4), the pre-drug control values of the $MAP_{90(CL300)}$, $MAP_{90(CL400)}$, effective refractory period and terminal repolarization period were 210±9, 226±13, 198±11 and 28±6 ms, respectively. After the low dose, no significant change was detected in these parameters. After the middle dose, the $MAP_{90(CL300)}$, $MAP_{90(CL400)}$ and effective refractory period were prolonged for 10–30 min, for 10–30 min and at 15 and 30 min, respectively. After the high dose, the $MAP_{90(CL300)}$,$MAP_{90(CL400)}$ and effective refractory period were further prolonged for 5–60 min. No significant change was detected in the terminal repolarization period.

In the pentobarbital group (n=4), the pre-drug control values of the $MAP_{90(CL300)}$, $MAP_{90(CL400)}$, effective refractory period and terminal repolarization period were 181±2, 191±5, 178±6 and 14±3 ms, respectively. After the low dose, no significant change was detected in these parameters. After the middle dose, the effective refractory period was prolonged for 5–30 min. Meanwhile, no significant change was detected in the $MAP_{90(CL300)}$, $MAP_{90(CL400)}$ or terminal repolarization period. After the high dose, the $MAP_{90(CL400)}$ and effective refractory period were prolonged for 30–60 min and for 5–60 min, respectively. Meanwhile, no significant change was detected in the $MAP_{90(CL300)}$ or terminal repolarization period. The extent of peak increment in the $MAP_{90(CL400)}$ in the halothane

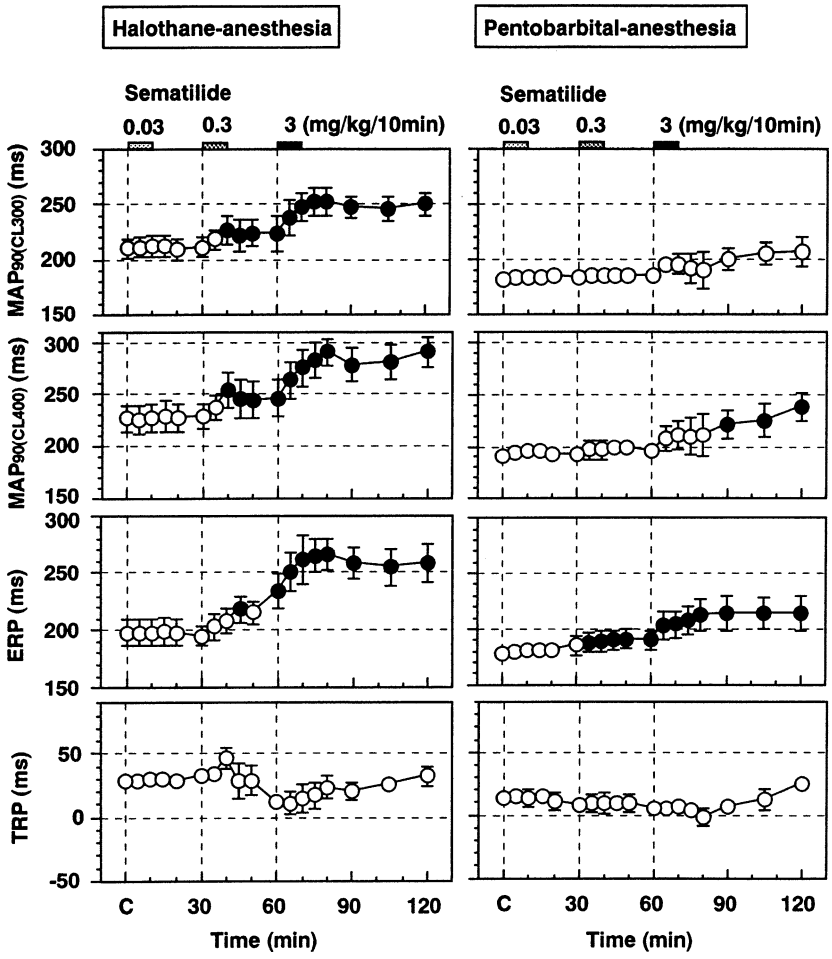

Fig. 4. Time courses of the duration of monophasic action potential at a level of 90% repolarization (MAP_{90}) at a pacing cycle length of 300 ms ($MAP_{90(CL300)}$) and 400 ms ($MAP_{90(CL400)}$), effective refractory period (ERP), and terminal repolarization period (TRP). The electrophysiological effects of sematilide under the halothane anesthesia (n=4) are shown in the left panel, whereas those under the pentobarbital anesthesia (n=4) are depicted in the right panel. Data are presented as mean±S.E.M. The closed symbols represent the significant differences from each control (C) value by P<0.05.

group was about 1.5 times greater than that of the pentobarbital group (+68 vs. +48 ms).

4. Discussion

In the present study, influence of halothane and pentobarbital on the cardiovascular system was compared using the in vivo canine model.

4.1. Comparison of basal cardiovascular variables under the halothane-anesthesia and pentobarbital-anesthesia (experiment 1)

4.1.1. Cardiohemodynamic variables

As shown in Table 1, the heart rate, blood pressure, cardiac contractility and cardiac output were lower under the halothane-anesthesia than pentobarbital-anesthesia, whereas the reverse is true for the left ventricular end-diastolic pressure. Previous in vitro studies have shown that the anesthetic concentration of halothane decreases the Ca^{2+} sensitivity of the myofilament, intracellular Ca^{2+} movements and Ca^{2+} currents in both the vascular smooth muscle cells and the ventricular myocytes (Buljubasic et al., 1992; Yamamoto et al., 1997; Su and Tang, 1998; Bosnjak et al., 1991; Davies et al., 2000a). In addition, suppressive effects on the vagal nerve transmission were demonstrated for pentobarbital (Chiba and Tsuboi, 2001). Therefore, currently observed difference of the basal cardiohemodynamic variables between the anesthetics may be associated with such cellular mechanisms.

4.1.2. Electrophysiological variables

Halothane as well as pentobarbital has been shown to inhibit the cardiac Na^+ channels, leading to the decrease in the maximum upstroke velocity of the action potential in the isolated myocardium (Ozaki et al., 1989; Nattel et al., 1990; Weigt et al., 1997; Wartenberg et al., 2001). In this study, no significant difference was detected in the intraventricular conduction, indicating that both anesthetics may suppress cardiac Na^+ channels in vivo to a similar extent.

The ventricular repolarization process was longer under the halothane-anesthesia than pentobarbital-anesthesia in this study. It should be noted that this phenomenon was observed during the ventricular pacing at fixed cycle lengths as well as the sinus rhythm. Previous in vitro electrophysiological studies have demonstrated that the clinical anesthetic concentration of halothane inhibits the I_{Kr}, the slowly activating delayed rectifier K^+ currents (I_{Ks}), inward rectifier K^+ currents (I_{K1}) and transient outward K^+ currents (I_{to}) in the isolated cardiomyocytes (Davies et al., 2000b; Stadnicka et al., 2000; Li and Correa, 2002, Shibata et al., 2004). On the other hand, pentobarbital has also been shown to suppress several cardiac K^+ channels including the I_{Kr}, I_{Ks}, I_{K1} and I_{to}, however, 2- to 35-folds high concentrations of its anesthetic free plasma concentrations in vivo (0.05–0.08 mM) is required to exert such electrophysiological effects (Nattel et al., 1990; Bachmann et al., 2002). These results suggest that the potency of the inhibitory effect on the cardiac K^+ channels may be greater for halothane than pentobarbital when compared at each anesthetic dose.

4.2. Comparison of the influence of halothane and pentobarbital on cardiovascular response to sematilide (experiment 2)

4.2.1. Dose of sematilide

In a previous study using a halothane-anesthetized canine model (Xue et al., 1996), maximum plasma drug concentrations after 0.3 mg/kg, i.v. of sematilide were approximately 1.0 μg/ml, which was close to clinically effective plasma drug concentration of 2.0 μg/ml (Wong et al., 1992). In addition, maximum plasma drug concentrations after 3 mg/kg, i.v. of sematilide were approximately 11 μg/ml in the halothane-anesthezed and 9 μg/ml in the pentobarbital-anesthetized dogs (Xue et al., 1996). Thus, the doses used in this study correspond to clinical sub-therapeutic to supra-therapeutic levels of plasma drug concentrations.

4.2.2. Cardiohemodynamic effects of sematilide

In the halothane-anesthetized dogs, the low and middle doses of sematilide hardly affected any of the cardiohemodynamic parameters, whereas the high dose exerted the negative chronotropic effect, which may be a common profile of selective I_{Kr} blockers (Nagashima et al., 1998; Satoh et al., 1999). In contrast, in the pentobarbital-anesthetized dogs, the negative chronotropic effect was observed from the low dose of sematilide, which could be in part explained by the higher pre-drug value of the heart rate. This negative chronotropic action itself can contribute to the QT interval prolongation, which may complicate the analysis of the effects of I_{Kr} blockers on the ventricular repolarization process (Nakaya et al., 1993).

4.2.3. Electrophysiological effects of sematilide

In the halothane- as well as pentobarbital-anesthetized dogs, sematilide prolonged the ventricular repolarization period without affecting the intraventricular conduction, which is similar to the effect of another selective I_{Kr} blocker dofetilide (Satoh et al., 1999). The extent of the prolongation of the ventricular repolarization period in the halothane-anesthetized dogs was greater than that in the pentobarbital-anesthetized dogs, although no significant difference has been demonstrated in pharmacokinetic profile of sematilide between the two anesthetic conditions (Xue et al., 1996). The more potent inhibitory effect of the halothane anesthesia on the cardiac K^+ channels may have decreased the repolarization reserve (Biliczki et al., 2002), which sensitized the heart for pharmacological I_{Kr} blockade, resulting in the excessive QT interval prolongation. In addition, in the preliminary experiment, we confirmed that an anti-cholinergic drug atropine did not modify the QT-prolonging effect of sematilide in the halothane-anesthetized dog, suggesting that suppressive effects of pentobarbital on the vagal nerve transmission (Chiba and Tsuboi, 2001) will not modify the QT-prolonging action of sematilide.

4.3. Conclusions

The halothane-anesthetized canine model is highly useful for predicting the in vivo I_{Kr} blocking property of new drugs.

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