原 著 (Original)

Effects of inhalational anesthetics and verapamil on atrioventricular conduction in dogs

——A comparative study of halothane, enflurane, isoflurane, and sevoflurane——

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Abstract

The interactions of halothane, enflurane, isoflurane, and sevoflurane with verapamil on atrioventricular (AV) nodal function were evaluated in dogs during atrial pacing. Thirty-four mongrel dogs were divided into five groups. Anesthesia was induced with ketamine and thiamylal and maintained with the following agents; 0.8% halothane, 1.6% enflurane, 1.2% isoflurane, or 1.7% sevoflurane with 50% nitrous-oxide in oxygen. We observed interactions between inhalational anesthetics and sequential iv administration of verapamil 0.01, 0.02, 0.07 mg/kg. Five dogs in control group (C) received verapamil in the same manner without inhalational anesthetic. There were prolongations of sinus cycle length (SCL) and functional refractory period (FRP) of the AV node after each anesthetic. SCL and FRP were further prolonged in a dose dependent manner after iv administration of verapamil. There was no difference of magnitude of prolongation due to verapamil between each anesthetic group and group C. In conclusion, all inhalational anesthetics studied and verapamil had additive interaction on AV conduction.

Key Words: Anesthetics: Volatile: enflurane, halothane, isoflurane, sevoflurane. Heart: conduction: atrio-ventricular. Pharmacology: verapamil

Introduction

Calcium entry blockers inhibit calcium influx into slow channels of exciting membranes resulting in vasodilatory[1-3], negative inotropic[2,3], and negative chronotropic[2,3] actions. These drugs have antiarrhythmic properties due to depressant effects on the impulse conduction system and are especially effective for treatment of supraventricular tachyarrhythmias, atrial fibrillation and atrial flutter[4]. Halogenated inhalational anesthetics also have depressant effects on myocardial contractility and impulse conduction system[5]. There are several reports concerning the combined effects of anesthetics and calcium entry blockers on hemodynamic function[6-10]. Halothane inhibits atrioventricular (AV) conduction and there are reports about the interaction between halothane and calcium entry blockers on the PR

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intervals[6-9]. Atlee et al demonstrated the combined effects of inhalation anesthetics and calcium entry blockers on AV conduction in spontaneously beating dog hearts[11]. However, it is important to compare electrophysiological variables using atrial pacing because atrioventricular conduction time is affected by heart rate. We have previously demonstrated the effects of halothane and calcium entry blockers, comparing verapamil, diltiazem, and nifedipine, on atrioventricular conduction in atrial paced dogs involving the functional refractory period of the AV node as well as the conduction time of the AV node[12]. There is little published information concerning such interactions with other inhalational agents. The present study was therefore undertaken to compare the combined effects of verapamil and halothane, enflurane, isoflurane, or sevoflurane on sinus and AV nodal function.

Materials and methods

The experimental protocol was approved by the Animal Care and Use Committee of Hokkaido University School of Medicine. Thirty-four mongrel dogs, weighing 7-13 kg, were randomly divided into five groups. They were anesthetized with ketamine 150 mg im and thiamylal 25 mg/kg iv and the tracheae were intubated. Ventilation was set to keep $ETCO_2$ between 35-40 mmHg as determined by capnography (NORMOCAP, Datex). Anesthesia was maintained with 50% nitrous-oxide in oxygen and pancuronium 2 mg im was used for muscle relaxation. A polyethylene catheter was placed in the thoracic aorta via the left femoral artery in order to measure systemic blood pressure using a pressure transducer (P23ID, Statham). Another catheter was inserted into the inferior vena cava via the left femoral vein for fluid infusion and drug administration. Arterial blood gas tensions and acid-base balance were periodically measured throughout the procedure. Esophageal temperature was maintained at 37±1°C by an infrared lamp and a warming pad.

Bipolar catheters were inserted through the right femoral vein and right external jugular vein to the heart in order to monitor the His bundle electrocadiogram and high right atrium electrocadiogram using a polygraph system (Nihonkoden). After a right thoracotomy, a bipolar catheter was sutured on the right outer atrial surface for pacing using a stimulator (SEN-3201, Nihonkoden). The following variables were mesured: sinus cycle length (SCL), atrium His (AH) and His ventricle (HV) intervals and functional refractory periods (FRP) of the AV node. The FRP of the AV node were obtained by the atrium scanning method in which the atria were driven at a basic cycle length (A1-A2) of 330 msec and premature atrial beats (A2) were elicited by progressively decreasing A1-A2 intervals up to the point of atrial refractoriness. The atrial, His bundle, and ventricular depolarizations during the basic atrial drive were defined as A1, H1, and V1 respectively. The depolarizations resulting from coupled premature atrial stimulation were defined as A2, H2, and V2 respectively. The FRP of the AV node were defined as the shortest H1H2 interval in response to two successive atrial impulses, both propagated through the AV node. All variables except SCL were measured in the basic cycle which was obtained by atrial pacing at 330 msec intervals. All data were recorded by a FM eight-channel recorder (SR-30, TEAC) for later measurement by a wave form controller (VY-640G, Nihonkoden) which was used in one msec resolution.

At least 30 min after the hemodynamic state was stabilized, control measurements of all variables were determined, then all measurements were repeated at an end-tidal concentration (modified Model 222, Datex) of each anesthetic of 1 MAC; 0.8% halothane (H), 1.6% enflurane (E), 1.2% isoflurane (I), or 1.7%

sevoflurane (S) in 50:50 nitrous-oxide: oxygen for each of the study groups. The effects of sequentially administered verapamil (0.01, 0.02, 0.07 mg/kg) were studied five minutes after each verapamil administration, which was injected in about one minute, in groups H, E, I, S, and C, respectively.

All values in the text and tables are given as mean±SEM. A Student paired t-test was used to analyze progressive changes in values within each group of dogs. Analysis of variance was used to determine whether there were significant differences between the four inhalational anesthetic groups.

Results

Mean arterial pressures (MAP) of the four inhalational anesthetic groups are shown in Table 1. There were no significant differences among groups in each phase of control, 1 MAC of inhalational anesthesia, and after cumulative administration of 0.1 mg/kg verapamil. Electrophysiological variables from groups H, E, I, S, and C are shown in the Fig. 1. There was no difference among control variables in any groups (ANOVA). Effects of 1 MAC inhalational anesthesia on SCL, AH and HV interval, and FRP of the AV node are shown in Table 2. All inhalational anesthetics prolonged SCL and FRP of the AV node, and in addition, halothane prolonged conduction time of the AV node (AH interval) (Fig. 1). As concerns the magnitude of changes, there were no significant difference among groups in all variables (Table 2).

—Interactions between inhalational anesthetics and verapamil—

In order to investigate interactions between inhalational anesthetics and verapamil, changes of SCL, AH and HV interval, and FRP of the AV node were calculated by subtraction of the value at 1 MAC of each inhalational anesthetic (groups H, E, I, and S) or control (group C) from the value of each dose of verapamil (Table 3). Changes of AH intervals and FRP of the AV node induced with cumulative doses of 0.1 mg/kg of verapamil with and without inhalation anesthetics were similar.

Discussion

When comparing effects of anesthetics on electrophysiological variables, it would be ideal to have a control state without anesthesia and then anesthetize the same animal with different anesthetics. However, it is important to compare electrophysiological variables using atrial pacing because atrioventricular conduction time is affected by heart rate. Since it is difficult to use atrial pacing in a conscious dog model, we elected to investigate dogs anesthetized with ketamine im and nitrous-oxide for our control determinations. This basal anesthesia was thought to have minimal effects on electrophysiological variables.

We selected doses of verapamil; 0.01, 0.02, 0.07 mg/kg sequentially administered so that the cumulative dose would be 0.1 mg/kg, which correspond to clinical doses used intravenously

Table 1. Mean arterial pressure during halothane, enflurane, isoflurane, and sevoflurane anesthesia and after verapamil.

Group	Agent (n)	Control	1 MAC Anesthesia	Verapamil 0.1 mg/kg
H	Halothane (7)	147± 7	109± 9*	94±7*
E	Enflurane (6)	140± 8	109±11*	105±7*
I	Isoflurane (6)	135±10	104± 9*	96±6*
S	Sevoflurane (7)	129± 4	103± 7*	96±3*

Mean±SEM (mmHg). Paired to control; * $p<0.05$. No significant differences among groups. Verapamil 0.1 mg/kg means the cumulative dose (0.01+0.02+0.07).

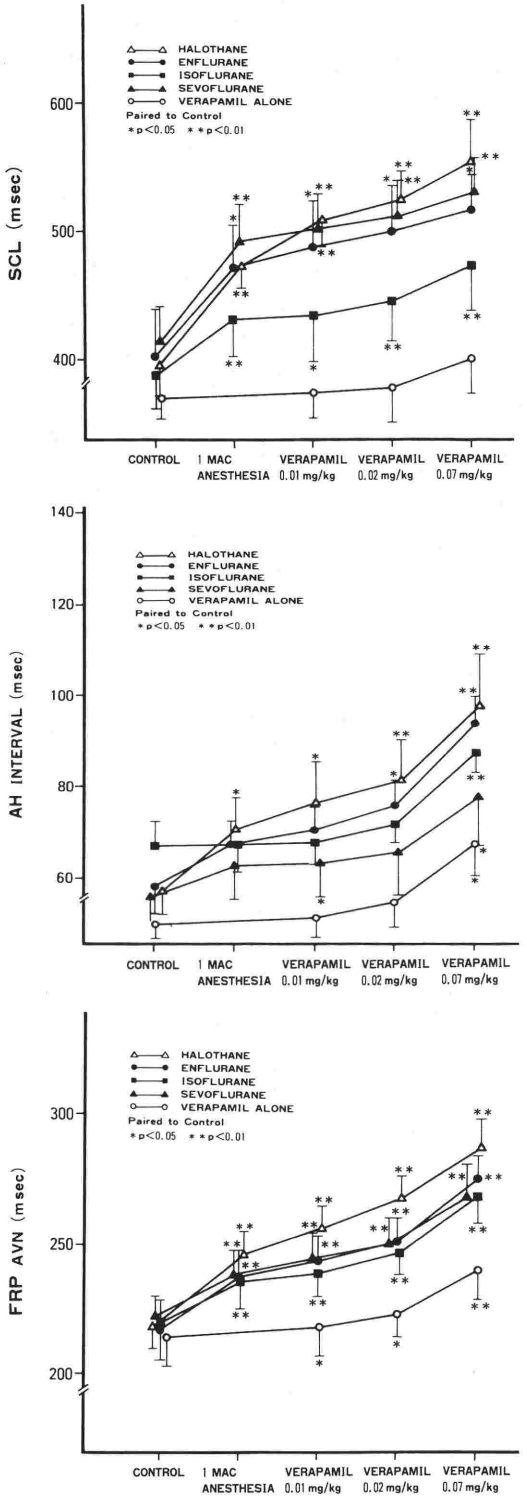

Fig. 1. Changes of SCL, AH interval, and FRP of AVN after 1 MAC inhalational anesthetics and sequential administration of verapamil.

during anesthesia. And we used the MAC values for man instead of those for the dog because these setting were thought to be clinical. All variables were measured 5 min after each iv injection during the expected maximum effect times of these injections. Nakaya and colleagues have reported that the greatest hypotensive effects occurred 2 min after iv administrations of calcium entry blockers (verapamil, diltiazem, nifedipine), and that the greatest effect on the impulse conduction system occurred 5–10 min after iv administraion in conscious dogs[2].

Regarding mean arterial pressure, the dogs tolerated this experimental model well. There was a dose dependent decrease in MAP of the same magnitude as noted in previously published investigations.

This study indicated that at a concentration of 1 MAC, all the inhalational anesthetics produced prolonged refractoriness of the AV node. Wilton et al reported that atrioventricular refractoriness was impaired by enflurane and halothane, but not isoflurane when compared with chloralose anesthesia[13]. The differences from our results concerning isoflurane may be due to the different methods used to measure refractoriness and also the the use of different anesthetics during control measurements.

In our study, only halothane prolonged conduction time of the AV node (AH interval) at 1 MAC anesthesia compared to control. Although the control value of the AH interval in group I was slightly high, there were no statistical differences in control values among groups. Atlee et al reported that both enflurane and halothane produced a similar prolongation of the AH interval[14]. In that study, however, basal heart rates were measured in spontaneously beating hearts, making the two studies not directly comparable. Atrioventricular conduction time becomes prolonged with increasing heart rate[15]; therefore, it is im-

Table 2. Changes from baseline of SCL, AH, HV, and FRP during 1 MAC anesthesia.

Group	Agent	SCL	AH	HV	FRP
H	HALOTHANE	76±14	13±4	0.9±0.3	28±5
E	ENFLURANE	69±23	9±5	0.2±0.5	20±4
I	ISOFLURANE	45±11	−0.3±2	0.4±0.2	16±2
S	SEVOFLURANE	78±13	7±3	−0.1±0.4	18±3

Mean±SEM (msec). SCL; Sinus Cycle Length, AH; Atrial-His Interval, HV; His-Ventricle Interval, FRP; Functional Refractory Period of AV node. No significant differences among groups in any variables.

Table 3. Changes from baseline of SCL, AH, and FRP due to sequential administration of verapamil combined with 1 MAC anesthesia.

			Verapamil		
Group	Agent (n)		0.01 mg/kg	0.02 mg/kg	0.07 mg/kg
SCL					
H	HALOTHANE	(7)	37±5	54± 6	82±17
E	ENFLURANE	(7)	14±4*	27±12*	44±15
I	ISOFLURANE	(7)	1±8*	12± 7*	41±12
S	SEVOFLURANE	(8)	10±3*	20± 3*	39± 6
C	VERAPAMIL ALONE	(5)	4±9*	8±14*	30±12
AH interval					
H	HALOTHANE	(7)	6±2	12± 2	27± 6
E	ENFLURANE	(6)	4±1	9± 1	27± 5
I	ISOFLURANE	(7)	1±1	5± 3	21± 4
S	SEVOFLURANE	(8)	0.4±1	4± 2	19± 5
C	VERAPAMIL ALONE	(5)	2±2	5± 4	18± 6
FRP of AVN					
H	HALOTHANE	(7)	10±1	22± 3	41± 6
E	ENFLURANE	(6)	6±1*	13± 2*	37± 5
I	ISOFLURANE	(7)	3±2*	11± 3*	34± 5
S	SEVOFLURANE	(8)	6±1*	13± 2*	33± 6
C	VERAPAMIL ALONE	(5)	4±1*	9± 3*	26± 5

Mean±SEM (msec) Paired to group H; * $p<0.05$ (ANOVA). SCL; Sinus Cycle Length, AH; Atrial-His Interval, FRP of AVN; Functional Refractory Period of AV node.

portant to compare AV conduction at the same heart rates, which can be achieved by pacing. In addition, the concentration of each anesthetic used in the two studies was different.

Many investigators have shown that verapamil increases heart rate in conscious dogs and humans due to baroreceptor reflex. Our results demonstrated that verapamil prolonged SCL in the control group, in agreement with our previous study[12]. In the present study, control measurements were performed during light anesthesia induced with ketamine im and thiamylal iv and maintained with 50% nitrous-oxide in oxygen. The slight prolongations of SCL induced by verapamil in group C may be related to the inhibitory effects of basal anesthesia on the baroreceptor reflex.

The present study indicates that verapamil and the four inhalational anesthetics studied produced additive prolongations of the SCL, AH interval, and FRP of the AV node respectively. A more recent report by Atlee et al also show-

ed that the prolongation of AH by verapamil during halothane and isoflurane anesthesia was additive[11]. Lynch and colleagues demonstrated that inhalation anesthetics (halothane, enflurane, isoflurane) and calcium entry blockers act in a similar fashion to interfere with calcium ion flux across excitable membranes[16-18] and explained why inhalational anesthetics and verapamil were additive. Hariman et al and Lehot et al showed that calcium chloride reversed the hemodynamic effects of verapamil but did not reverse its electrophysiological effects in the presence or absence of halothane[19,20].

In conclusion, halothane, enflurane, isoflurane, and sevoflurane had inhibitory effects on AV nodal function. Verapamil and the inhalational anesthetics had additive effects on AV conduction when inhalational anesthetics were used in 1 MAC concentration.

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