Effects of Halothane and Calcium Entry Blockers on Atrioventricular Conduction

— A Comparative Study of Verapamil, Diltiazem, and Nifedipine —

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The effects of halothane on AV nodal function were evaluated in dogs with verapamil, diltiazem, or nifedipine during atrial pacing using the technique of His-bundle electrocardiography. Fifty-one mongrel dogs were divided into six groups. Anesthesia was induced with ketamine 100 mg im. and thiamylal 25 mg/kg iv. The animals were intubated and mechanically ventilated at normocapneic levels. Anesthesia was maintained with 50% nitrous-oxide in oxygen with pancuronium 2 mg im. Dogs in groups I, III, and V were anesthetized with 0.8% halothane and 50% nitrous-oxide in oxygen. We observed interactions between halothane and intravenous administration of either verapamil 0.1 mg/kg, diltiazem 0.15 mg/kg, or nifedipine 0.01 mg/kg respectively. Dogs in groups II, IV, and VI were administered either verapamil, diltiazem, or nifedipine iv without halothane. There were prolongations of sinus cycle length (SCL) (414 ± 10 to 542 ± 19 msec.), atrium-His (AH) interval (73 ± 3 to 97 ± 5 msec.), and functional refractory period (FRP) of the AV-node (227 ± 5 to 260 ± 5 msec.) in halothane anesthesia in groups I, III, and V. There were more prolongations of these variables after iv administration of verapamil (SCL; 617 ± 35, AH; 118 ± 7, FRP of the AV node; 311 ± 4) and diltiazem (SCL; 554 ± 19, AH; 118 ± 12, FRP of the AV node; 283 ± 12) but no prolongations after nifedipine (SCL; 533 ± 19, AH; 99 ± 8, FRP of the AV node; 272 ± 9). Comparing effects of calcium entry blockers with and without halothane in groups I and II, III and IV, or V and VI, there were additive depressing effects of halothane with either verapamil or diltiazem on AV nodal function. And there is a difference between the effects of nifedipine on SCL with and without halothane. (Key words: Anesthetics, halothane, atrioventricular conduction, verapamil, diltiazem, nifedipine.)

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Calcium entry blockers have been used to treat hypertension and dysrhythmias during anesthesia since Brichard et al. reported the efficiency of these drugs in 1970[1]. Calcium entry blockers inhibit calcium influx into the slow channel of excitable membranes which produce extreme vasodilative[2–4], inotropic[3,4], and chronotropic[3–6] actions. These drugs have antiarrhythmic actions due to depressant effects on impulse conduction system, especially effective for supraventricular tachyarrhythmias, atrial fibrillation and atrial flutter[7–11]. Halothane, i.e. halogenated inhalation anesthetic also has de-

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pressant effects on myocardial contractility and impulse conduction system[12–16]. There are several reports about combined effects of halothane and calcium entry blockers on the hemodynamics[1,17–26]. Since it is well known that halothane inhibits atrioventricular (AV) conduction and there are some reports about the interaction between halothane and calcium entry blockers on the PR intervals[17,19–23], it will be necesary to evaluate the combined effects of halothane and calcium entry blockers on AV conduction for safety use of these drugs. The present study was designed to compare the combined effects of halothane and either verapamil, diltiazem, and nifedipine on sinus and AV nodal function.

Methods

Fifty-one mongrel dogs, weighing 7-13 kg, were randomly divided into 6 groups. Dogs were anesthetized with ketamine 150 mg im. and thiamylal 25 mg/kg iv. and tracheae were intubated. Ventilation was set to keep Pa_{CO_2} about 35–40 mmHg. Anesthesia was maintained with 50% nitrous-oxide in oxygen and pancuronium 2 mg im. A polyethylene catheter was placed into the thoracic aorta via the left femoral artery in order to measure systemic blood pressure. Another catheter was inserted in the inferior vena cava for infusion and drug administration. Bipolar catheters were inserted through the right femoral vein and right external jugular vein in order to monitor the His bundle electrocardiogram and high right atrium electrocardiogram. After a right thoracotomy, a bipolar catheter was sutured on the right atrium for the atrial pacing. The following variables were measured: sinus cycle length (SCL), atrium His (AH) and His ventricle (HV) intervals and functional and effective refractory periods (FRP and ERP) of the AV node. FRP and ERP of the AV node were obtained by the atrium scanning method in which the atria were driven at a basic cycle length (A1-A2) and premature atrial beats (A2) were elicited at 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. And these depolarizations resulting from coupled premature atrial stimulation were defined as A2, H2, and V2, respectively. The definition of ERP of the AV node was the longest A1A2 interval at which A2 does not conduct to the bundle of His. And FRP of the AV node was 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 is obtained by atrial pacing on 330 msec interval.

After control measurements, all measurements were repeated during inspiration of 0.8% halothane and 50:50 nitrous-oxide: oxygen (in groups I, III, and V). Then, the effects of either verapamil (0.1 mg/kg), diltiazem (0.15 mg/kg) or nifedipine (0.01 mg/kg) were studied in groups I, III, and V, respectively. In groups II, IV, and VI, effects of each calcium entry blocker of the same dose as groups I, III, and V, were studied without halothane administration.

All values in the text, tables, and figures are given as mean ± SEM. A Student paired t-test was used to analyze progressive changes in values within each group of dogs, while a Student non-paired t-test was used to compare changes between values of each calcium entry blocker with and without halothane. Analysis of variance was used to determine if there were significant differences among three calcium entry blockers.

Values of ERP of the AV node were not analyzed by statistical techniques since it was often difficult to measure ERP of the AV node accurately when an impulse was blocked in the atrium earlier to the AV node.

Results

All variables measured in the present study are shown in table 1. There is no difference between control values in all groups.

Halothane prolonged SCL (fig. 1). Diltiazem with halothane prolonged SCL compared to halothane alone. Changes of SCL induced by verapamil with and without

Table 1. Sinus cycle length (SCL), atrial-His interval (AH), His-ventricle interval (HV), functional refractory period (FRP), and effective refractory period (ERP) of atrioventricular node (AVN) in all groups

Group (n)		SCL	AH	HV	FRP of AVN	ERP of AVN
I (7)	Control	430 ± 25	68 ± 5	23 ± 2	223 ± 7	155 ± 3
	Halothane	597 ± 52**	96 ± 6**	24 ± 2	269 ±6**	185 ± 9
	Verapamil	617 ± 36**	118 ± 7$^{**}_{**}$	26 ± 2$^{**}_{**}$	311 ± 4$^{**}_{**}$	251 ± 7
II (7)	Control	390 ± 25	63 ± 7	23 ± 1	215 ± 10	154 ± 2
	Verapamil	425 ± 21	96 ± 15*	23 ± 1	250 ± 13**	179 ± 11
III (9)	Control	401 ± 12	74 ± 6	25 ± 1	224 ± 10	158 ± 8
	Halothane	523 ± 24**	99 ± 10**	26 ± 1*	248 ± 10**	184 ± 12
	Diltiazem	554 ± 19$^{**}_{**}$	118 ± 12$^{**}_{**}$	28 ± 1$^{**}_{**}$	283 ± 12$^{**}_{**}$	215 ± 16
IV (5)	Control	426 ± 20	64 ± 7	21 ± 1	206 ± 4	153 ± 3
	Diltiazem	448 ± 20	85 ± 8**	21 ± 2	233 ± 4**	164 ± 3
V (8)	Control	414 ± 16	76 ± 7	26 ± 1	234 ± 10	169 ± 9
	Halothane	516 ± 19**	96 ± 8*	26 ± 2	267 ± 10**	202 ± 15
	Nifedipine	534 ± 19**	99 ± 8*	28 ± 2	272 ± 9**	202 ± 14
VI (5)	Control	418 ± 26	74 ± 3	22 ± 0.4	209 ± 3	154 ± 4
	Nifedipine	394 ± 22	75 ± 4	23 ± 1	206 ± 3	141 ± 4

Mean ± SEM (msec) Paired to Control; * $P<0.05$ ** $P<0.01$
Paired to Halothane (in groups I, III, and V); ⋆ $P<0.05$ ⋆⋆ $P<0.01$

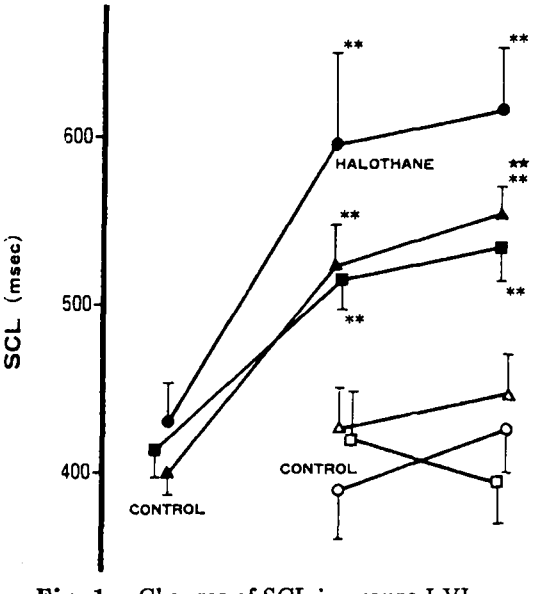

Fig. 1. Changes of SCL in groups I-VI.
In groups I, III, and V, control → halothane → calcium entry blockers; verapamil (•), diltiazem (▲), nifedipine (▪). In groups II, IV, and VI, control → calcium entry blockers; verapamil (○), diltiazem (△), nifedipine (□). * $P<0.05$, ** $P<0.01$ (paired to control). ⋆ $P<0.05$, ⋆⋆ $P<0.01$ (paired to halothane)

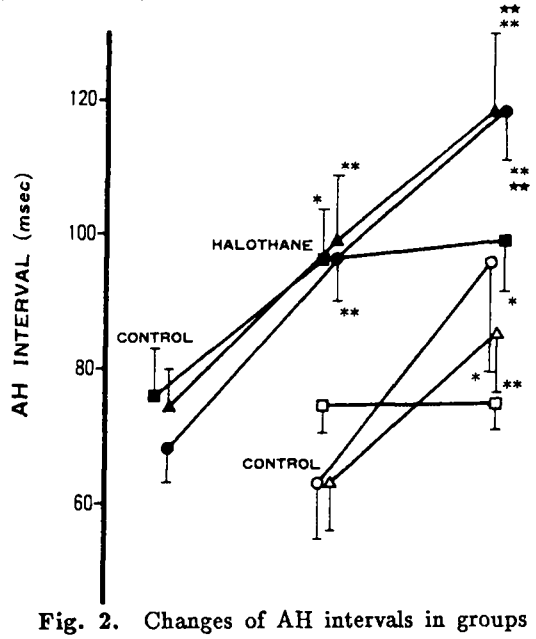

Fig. 2. Changes of AH intervals in groups I-VI.
In groups I, III, and V, control → halothane → calcium entry blockers; verapamil (•), diltiazem (▲), nifedipine (▪). In groups II, IV, and VI, control → calcium entry blockers; verapamil (○), diltiazem (△), nifedipine (□). * $P<0.05$, ** $P<0.01$ (paired to control). ⋆ $P<0.05$, ⋆⋆ $P<0.01$ (paired to halothane)

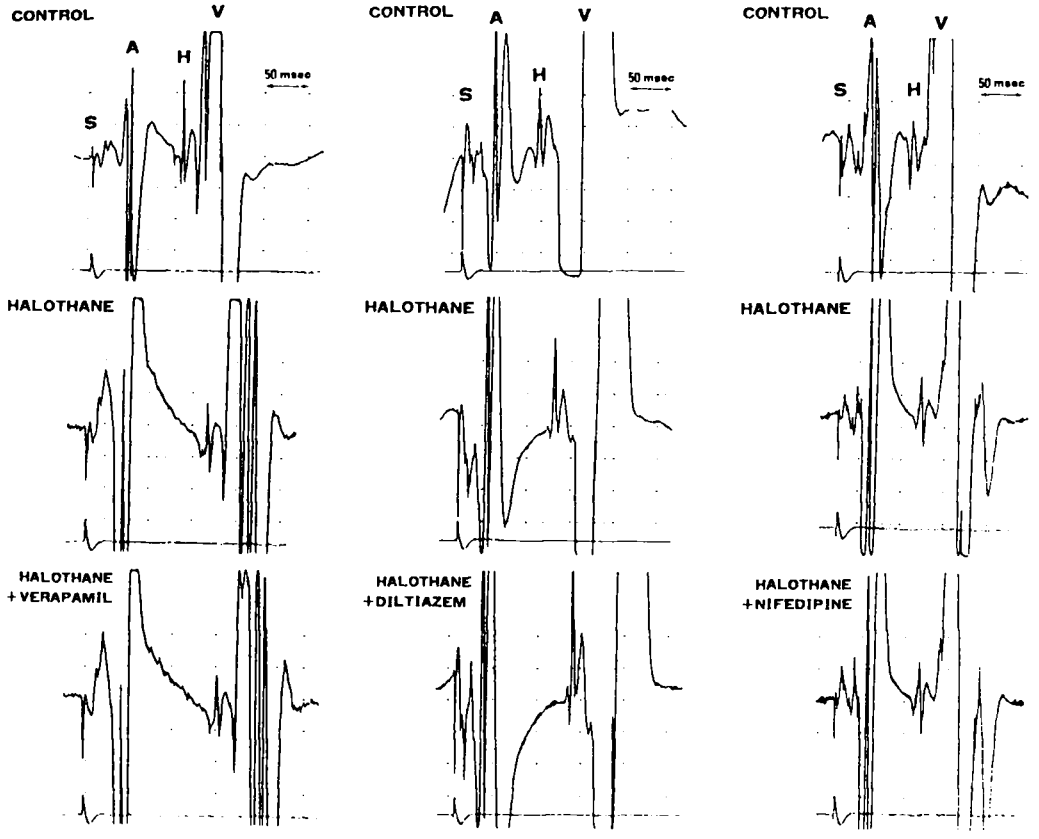

Fig. 3. Typical His bundle electrocardiograms in groups I, III, and V.
S: stimulation artifact. A: atrium depolarization. H: His bundle depolarization. V: ventricle depolarization.

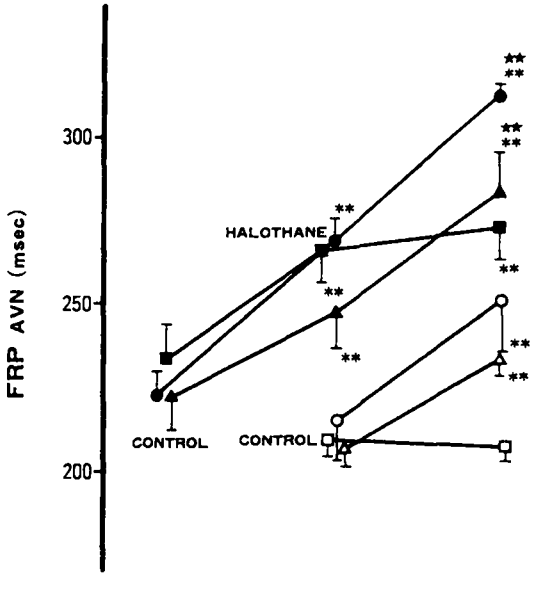

Fig. 4. Changes of FRP of the AV node in groups I-VI.

In groups I, III, and V, control → halothane → calcium entry blockers; verapamil (●), diltiazem (▲), nifedipine (■). In groups II, IV, and VI, control → calcium entry blockers; verapamil (○), diltiazem (△), nifedipine (□). * $P<0.05$, ** $P<0.01$ (paired to control). ⋆ $P<0.05$, ⋆⋆ $P<0.01$ (paired to halothane)

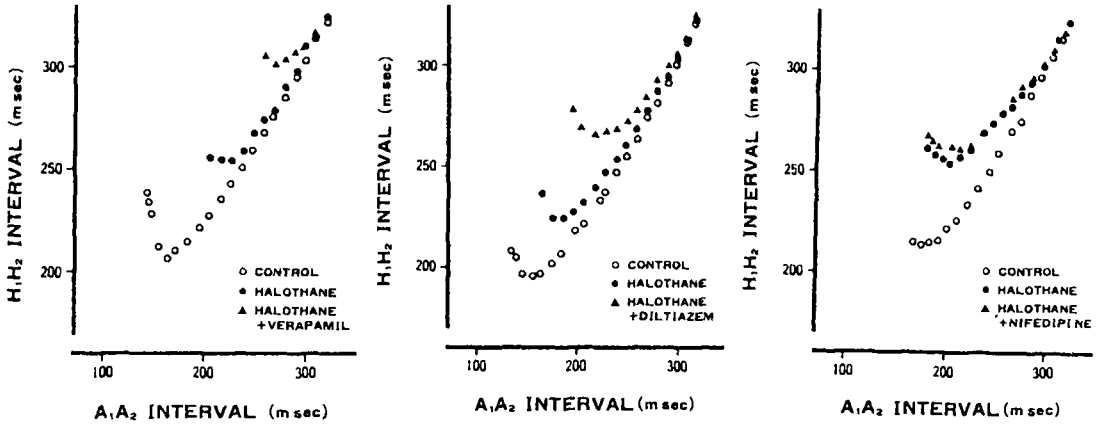

Fig. 5. Relationship of A1A2 intervals and H1H2 intervals in typical dogs in groups I, III, and V (details in text).

Table 2. Gradients of effects of calcium entry blockers with and without halothane

Calcium entry blockers		Group	SCL	AH	FRP of AVN
verapamil	with halothane	I	20 ± 22	22 ± 5	43 ± 4
	without halothane	II	35 ± 21	33 ± 9	35 ± 4
diltiazem	with halothane	III	31 ± 9	19 ± 4	35 ± 5
	without halothane	IV	22 ± 21	22 ± 3	27 ± 4
nifedipine	with halothane	V	18 ± 10*	3 ± 3	6 ± 4
	without halothane	VI	−24 ± 9	2 ± 2	−3 ± 2

Mean ± SEM (msec) Paired to "without halothane" *$P<0.05$

halothane were not significant. Although nifedipine without halothane shortened SCL, nifedipine with halothane prolonged SCL.

AH intervals were prolonged by either halothane, verapamil, or diltiazem (figs. 2,3). Figure 3 shows real records of His bundle electrocardiograms of typical dogs in groups I, III, and V. Nifedipine has no effect on AH intervals with or without halothane.

FRP of the AV node was prolonged by either halothane, verapamil, or diltiazem (figs. 4, 5). Figure 5 shows effects of halothane, verapamil, diltiazem, and nifedipine on H1H2 intervals and A1A2 intervals of typical dogs in groups I, III, and V which were obtained by the atrium scanning. Nifedipine has no effect on FRP of the AV node with and without halothane.

HV intervals were slightly prolonged by halothane in group III. Either verapamil or diltiazem with halothane prolonged HV intervals only in a few milliseconds (table 1).

Interactions between halothane and calcium entry blockers

In order to investigate interactions between halothane and calcium entry blockers, changes of either SCL, AH interval, or FRP of the AV node were calculated by subtraction of the value of halothane (groups I, III, and V) or control (groups II, IV, and VI) from the value of each calcium entry blocker. Changes of AH intervals and FRP of the AV node induced verapamil or diltiazem with and without halothane were similar. This might represent the additive effects of halothane and either verapamil or diltiazem on AV conduction. There was a significant difference between changes of SCL in nifedipine with and without halothane ($P<0.05$,

table 2).

Discussion

There are many reports about electrophysiologic properties of calcium entry blockers and clinical evaluations of these drugs for arrhythmias[2-11]. In this study, we selected these doses of verapamil, diltiazem, and nifedipine which were expected to have the similar hypotensive effects. These doses of calcium entry blockers are clinical doses used intraveously during anesthesia. Although there was no difference between blood pressures 5 min after intravenous administration of these drugs, nifedipine had the most hypotensive effects immediately after bolus injection. Nakaya and colleagues reported that there were the most hypotensive effects 2 min after iv administrations of calcium entry blockers, and the most effective on impulse conduction system 5–10 min after iv administrations in conscious dogs[3]

Halothane prolonged either SCL, AH interval, or FRP of the AV node in groups I, III, and V (figs. 1,2,4). In group III, halothane prolonged HV interval. These results consist with many other reports[12-16]

There are prolongations in AH intervals and FRP of the AV node induced by either verapamil or diltiazem in groups I, II, III, and IV (fig. 2). In group III, diltiazem prolonged SCL. Verapamil with and without halothane and diltiazem without halothane and even nifedipine with halothane prolonged SCL to some extent, but these effects are not significant (fig. 1). Comparing these calcium entry blockers, there is a difference on FRP of the AV node between verapamil and nifedipine in groups II and VI ($P<0.05$ ANOVA). These results are similar to results reported previously by other investigators[3-6]. Although many investigators showed that verapamil or diltiazem increases heart rate in conscious dogs and in awake humans as does nifedipine, our results showed that verapamil or diltiazem alone prolongs SCL. In the present study, control state was performed under a rather light anesthesia induced with ketamine im., thiamylal iv. and maintained with 50% nitrous-oxide with oxygen. The prolongations of SCL induced by verapamil or diltiazem in groups II or IV may be related to the inhibitory effects of basal anesthesia on the baroreceptor reflex.

In the present study, we used ketamine, thiamylal, and nitrous-oxide with pancuronium for basal anesthesia. Ketamine is used in the cardiac anesthesia, especially for the child who is uncooperative, crying, or struggling[27]. We defined that these drugs had a little effects on electrophysiologic parameters (unpublished observations). Then our experimental model was well simulated the clinical anesthesia. Our results indicated that halothane and either verapamil or diltiazem have an additive effect on AV conduction (figs. 1,2,4 & table 2). Lynch and colleagues showed that halothane and calcium entry blockers act similarly to interfere with calcium ion flux across excitable membranes[28]. There is considerable interaction between halothane and nifedipine on SCL (table 2). Hariman et al. and Lehot et al. showed that calcium chloride reversed the hemodynamic effects of verapamil but did not reverse the electrophysiologic effects of verapamil either with and without halothane[29,30]. These data suggest that risks may exist during use of calcium entry blockers and halothane anesthesia.

In conclusion, 0.8% halothane anesthesia has strong depressant effects on sinus automaticity and AV conduction compared with basal anesthesia alone. Verapamil and diltiazem combined with halothane had more depressant effects on AV conduction compared with halothane alone. Although nifedipine had little effect on electrophysiological changes, there was significant interactions on sinus automaticity between halothane and nifedipine.

These results may suggest that calcium entry blockers should be used with caution during halothane anesthesia because the interaction of these drugs may cause AV block, extreme hypotension, or extreme bradycardia in clinical anesthesia.

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