Anesthesiology
68:519–528, 1988

Conscious State Comparisons of the Effects of the Inhalation Anesthetics and Diltiazem, Nifedipine, or Verapamil on Specialized Atrioventricular Conduction Times in Spontaneously Beating Dog Hearts

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The effects of enflurane (ENF), halothane (HAL), and isoflurane (ISO) on specialized atrioventricular (AV) conduction times were contrasted to awake (control) in 22 chronically instrumented dogs. Dogs were studied with and without diltiazem (DIL), nifedipine (NIF), vehicle for NIF (VEH), or verapamil (VER). These calcium channel blockers (CCB) were administered iv to achieve clinically effective steady-state plasma levels in awake dogs. CCB plasma levels in awake dogs, subsequently anesthetized with ENF (N = 10), HAL (N = 10), or ISO (N = 11), were: DIL = 94 ± 13 to 124 ± 9 ng/ml, NIF = 4 ± 1 to 7 ± 2 ng/ml, VER 108 ± 23 to 147 ± 9 ng/ml. Anesthetized dogs had approximate two-fold increases in plasma levels of DIL or VER. There was no anesthetic effect on plasma levels for NIF. In the absence of CCBs, HAL increased AV nodal conduction time (AVN) compared to awake. There was a 4–10% increase in His-Purkinje (HP) and ventricular (VENT) conduction time with each anesthetic. The CCBs did not alter HP or VENT in awake dogs, but AVN was increased 15–23% by DIL and 28–38% by VER. Three of ten dogs with VER developed complete heart block or AV junctional escape rhythm at each level of ENF. One dog with VER developed type I, 2° (Wenckebach) AV block at each level of HAL and ISO. No dogs with DIL had heart block or escape rhythms during anesthesia. In anesthetized dogs without heart block or escape rhythms, the increase in AVN with VER ranged from 46 to 69%, and with DIL from 36 to 55%. The CCB had no added effects on HP or VENT with any anesthetic. Finally, there were no effects of NIF alone or with the anesthetics on specialized conduction that could not be attributed to VEH. The authors conclude that with the inhalation anesthetics, antiarrhythmic plasma levels of DIL or VER prolong AV nodal most compared to infranodal conduction time. Additionally, heart block or escape rhythms appear more likely with VER and any of the potent inhalation anesthetics. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: arrhythmias; conduction; electrocardiography. Pharmacology: diltiazem; nifedipine; verapamil.)

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Received from the Department of Anesthesiology, University of Wisconsin Center for Health Sciences, Madison, Wisconsin. Accepted for publication November 4, 1987. Supported in part by NIH GM-25064 and grants-in-aid from Anaquest, G.D. Searle, Marion Laboratories, and the University of Wisconsin Anesthesiology Department of Research and Development Fund. Presented in part at Annual Meetings of the American Society of Anesthesiologists, October 1986 and 1987.

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COMPARED TO AWAKE, clinically relevant levels (1.2–2.3 MAC equivalents) of enflurane, halothane, and, to a lesser extent, isoflurane, have been shown to prolong atrioventricular (AV) nodal, and ventricular specialized His-Purkinje conduction times in spontaneously beating hearts of chronically instrumented dogs.[1] Most prolongation of conduction occurred with the onset of anesthesia, with little added depression due to increased level of anesthesia. Of the currently available calcium channel blocking drugs, diltiazem and verapamil prolong AV nodal, but not His-Purkinje conduction.[2] Moreover, both drugs are likely to be effective against supraventricular tachyarrhythmias following intravenous administration.[3] Any direct effect of nifedipine to prolong AV nodal conduction time is likely to be opposed by increased sympathetic tone provoked by nifedipine's peripheral vascular effects.

Of the available studies of cardiovascular interactions between the potent volatile inhalation anesthetics and calcium channel blockers, none have compared individual or combined drug effects on specialized AV conduction times (AV nodal, His-Purkinje, ventricular). Nor have they contrasted drug effects on conduction to those in a conscious, non-sedated state. Knowledge of individual and combined drug effects on specialized conduction times is important for the management of heart block. Drug-impaired conduction at the AV node may be reversed by pharmacologic means (atropine, isoproterenol). In contrast, infranodal block due to impaired His-Purkinje or ventricular conduction is not easily reversed by drugs, and is best managed by temporary pacing. While several studies have reported P-R interval prolongation, AV block, or AV junctional rhythm with the inhalation anesthetics and calcium channel blockers,[4–7] these studies did not discriminate independent or interactive drug effects on specialized conduction times. Additionally, two of these studies lacked an awake control.[6,7] To ascertain independent and interactive effects of the inhalation anesthetics and the calcium channel blockers on specialized cardiac conduction, we have examined the effects of these drugs on specialized AV conduction times in a dog model suitable for chronic and awake His bundle re-

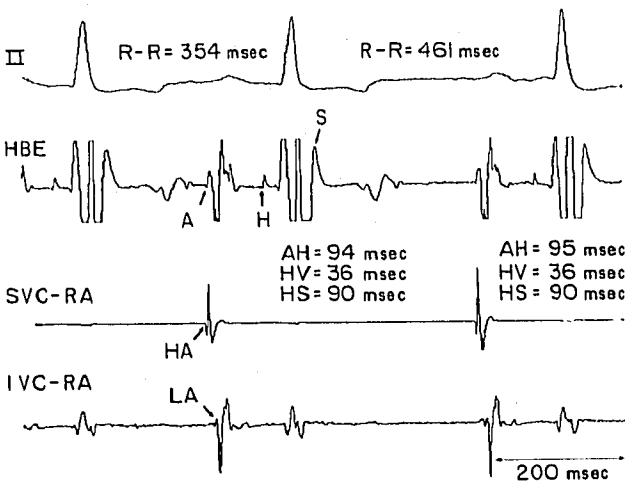

FIG. 1. Surface ECG lead II (II) is displayed simultaneously with the His bundle electrogram (HBE) and signals from electrodes located at the junction of the right atrium with the superior vena cava (SVC-RA) and inferior vena cava (IVC-RA). The dog was awake and had pronounced spontaneous cycle length (SCL) variation—sinus arrhythmia (R-R intervals here of 354 and 461 msec). AV nodal (AH), His-Purkinje (HV), and ventricular (HS) conduction times were measured for the second of two beats used to determine SCL. Finally, note that high right atrial activation (HA) precedes (by 14 msec) low right atrial activation (LA), indicating the sinus origin of both beats.

cording.[8] Clinically relevant anesthetic levels (1.2 and 1.6 MAC) were selected, and dosing with the calcium channel blockers was designed to produce plasma diltiazem or verapamil levels effective against supraventricular tachyarrhythmias,[2] or with nifedipine, a 10–20% reduction in systolic arterial pressure.

Methods

Instrumentation

Mongrel dogs of either sex (10–21 kg) were prepared for chronic His bundle recording according to our previously described method.[8] Briefly, a right thoracotomy was performed at the third or fourth interspace during thiopental, halothane, nitrous-oxide anesthesia. Bipolar, platinum-iridium, ring electrodes were sutured to the epicardial surface of the right atrium at its junction with the superior and inferior vena cavae, and the right ventricular apex. A unipolar, insulated, platinum-iridium needle electrode was advanced into the interatrial septum from the aortic root for recording the His bundle electrogram (His electrode). The His electrode was referenced to a unipolar ring electrode sutured to the adventitia of the proximal ascending aorta. Wires leading from the electrode pairs were tunneled subcutaneously to a 12-pin connector assembly (Microtech®) located between the scapulae. Later, on experimental occasions, a 4 Fr catheter (Cook®) was inserted percutaneously under local anesthesia (1% lidocaine) into the femoral artery. It was used for arterial sampling and recording arterial pressure (Statham® P23 Db).

AV Conduction Measurements

Electrically shielded, 12-strand conduction cable (Microtech®) led from the connector assembly to ECG recording amplifiers (E for M/Honeywell® VR-12). The surface ECG (lead II) was displayed simultaneously with filtered signals (30–250 Hz) from the intracardiac electrodes (fig. 1). Outputs from each of the ECG amplifiers were recorded (1⅞ ips) along with voice input on an 8-channel FM recorder (Vetter®) for later measurement of specialized AV conduction time intervals. Specialized AV conduction times—AV nodal (A-H interval), His Purkinje (H-V interval), and total ventricular conduction time (H-S interval)—are defined elsewhere,[1,8] and were measured with one millisecond resolution (Norland® 3001, digital processing oscilloscope). All measurements of conduction times were made during spontaneous rhythm. Heart rate (beats/min) was calculated from spontaneous cycle length (SCL, msec).‡‡ All dogs studied in the conscious state, including those studied with all of the calcium channel blockers, and with the vehicle for nifedipine, had pronounced SCL variation; that is, sinus arrhythmia (cycle length variation = 200–600 msec or more in some dogs). Consequently, SCL in conscious dogs was estimated by taking the average of two representative long and short cycle length beats during a 2-min period of sinus arrhythmia. Sinus arrhythmia was abolished by anesthesia (cycle length variation less than 100 msec). In anesthetized dogs, SCL was the average of four randomly selected cycles during spontaneous (sinus) rhythm. In both awake and anesthetized dogs, specialized AV conduction intervals were measured for the second of the two beats used to determine SCL (fig. 1).

Experimental Procedure

Instrumented dogs (N = 22) were used for testing when similar control (awake) values for spontaneous cycle length and specialized AV conduction times were obtained on successive, weekly test occasions. This was, in all cases, within 4 weeks following electrode implantation. During the period for stabilization, dogs were

‡‡ Heart rate = 60,000/SCL.

accustomed to the laboratory environment and trained to stand quietly in a restraining harness (Controller® Animal Restraining Devices, Inc., Farmington Hill, MI). All awake testing was performed with the dog in the standing harness.

Dogs were assigned (randomized order) to be tested with one of the three anesthetics—enflurane (ENF), halothane (HAL), or isoflurane (ISO). Experiments with each agent were performed on five, once-weekly test occasions. On test occasions, animals were tested with the anesthetic alone, or with anesthetic in the presence of diltiazem (DIL), nifedipine (NIF), verapamil (VER), or anesthetic with the vehicle (VEH) for nifedipine (fig. 2). The order of testing with calcium channel blockers or vehicle was also randomized. Upon completion of testing with each anesthetic, testing proceeded to one of the other two anesthetics, and so forth. Two dogs were tested with all three anesthetics and all possible combinations of calcium channel blockers—a total of 15 experiments. The remaining dogs were tested with at least one anesthetic agent with all possible calcium channel blockers—a minimum of five experiments.

On each test occasion, 15–20 min were allowed for the animal to become adjusted to the standing, restraining harness. Then, measurements were made in the conscious state (control) of arterial pressure and conduction times. After control measurements, dosing with the calcium channel blockers or vehicle for nifedipine began. Twenty-five to 35 min following calcium channel blockers or vehicle, awake measurements were repeated. Following testing in the conscious state, anesthesia was induced by mask with the desired anesthetic agent delivered in oxygen. The trachea was intubated and the dog mechanically ventilated to keep the end-tidal level of CO_2 (Beckman® LB-2) between 33 and 38 mmHg. Anesthetics were administered to achieve end-tidal anesthetic levels (Beckman® LB-2) equivalent to 1.2 and 1.6 MAC for the dog.[9] These levels, also randomized, were 2.6 and 3.5% for ENF, 1.0 and 1.4% for HAL, and 1.8 and 2.4% for ISO. Measurements of arterial pressure, heart rate, and conduction times were made at each of the two anesthetic end-tidal levels. Measurements during anesthesia were made at the 75–85- and 105–115-min time periods following dosing with calcium channel blockers or vehicle. Heart rate and blood pressure were stable for at least 10 min prior to measurements. Esophageal temperatures ranged between 36.5 and 38.5° C. During anesthetic equilibration and testing, which lasted approximately 2 h, animals received no fluid other than that required for infusion of drugs (approximately 100 ml), or heparinized saline (4 units/ml) flush for vascular catheters (less than 50 ml). Corrections, *e.g.*, Na bicarbonate or potassium chloride, were not made for abnormal blood gas or electrolyte values.

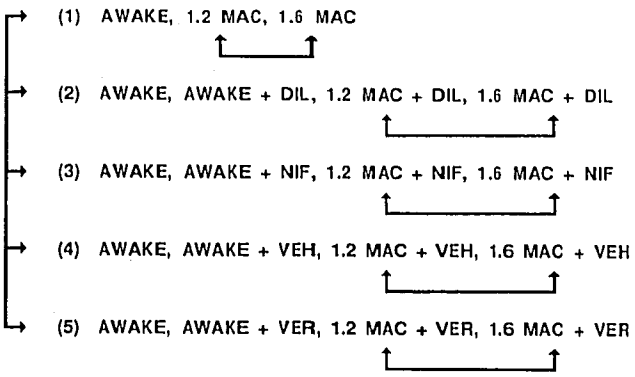

FIG. 2. Schematic for testing procedure indicating sequences for testing of with each anesthetic both with and without calcium channel blockers. 1.2 and 1.6 MAC indicates the anesthetic (enflurane, halothane, isoflurane) levels tested. DIL = diltiazem; NIF = nifedipine; VEH = vehicle for nifedipine; VER = verapamil. ↑—↑ indicates randomization. In experiments with calcium blockers or VEH, measurements of blood pressure and conduction time intervals were made at 25–35 min (AWAKE), 75–85 min (first anesthetic level), and 105–115 min (second anesthetic level).

CALCIUM CHANNEL BLOCKER ADMINISTRATION AND ASSAYS

Diltiazem (DIL) and verapamil (VER) were dissolved in 5% dextrose and water (0.5 mg/ml). For both DIL and VER, a bolus dose (over 10 min) of 140 $\mu g \cdot kg^{-1}$ was followed by a continuous infusion (lasting 115 min) of 8.5 $\mu g \cdot kg \cdot min^{-1}$. Nifedipine (NIF) was dissolved in vehicle (0.1 $mg \cdot ml^{-1}$) with the following composition: 15.0 gm ethanol, 15.0 gm polyethylene glycol, and sterile water q.s. 100 ml. For NIF, the bolus dose (over 10 min) was 20 $\mu g \cdot kg^{-1}$ and the continuous infusion (lasting 115 min) was 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$. For experiments with vehicle for NIF, a comparable volume (bolus = 10 ml; infusion = about 100 ml) was infused to that which would have been given with NIF.

Dosing schedules for the calcium channel blockers were selected based on pharmacokinetic data supplied by Patricia Kapur, M.D. (University of California, Los Angeles), R. G. McAllister, M.D. (Glaxo, Inc., Research Triangle Park, NC), G. D. Searle, Co., Marion and Pfizer Laboratories (all personal communications). These doses, in pilot studies, had provided stable plasma levels in awake dogs, and only small changes in cardiovascular function: DIL = 10–20 msec increase in the P-R interval of the surface electrocardiogram (ECG, lead II); NIF = 10–30 mmHg decrease in systolic arte-

TABLE 1. Spontaneous Heart Rate, Specialized Atrioventricular Conduction Times, and Mean Arterial Pressure in Conscious, Nonsedated Dogs. All Values are Mean ± SEM with the Number of Dogs Shown in Parentheses

	Enflurane	Halothane	Isoflurane
HR	112 ± 9 (10)	104 ± 3 (10)	111 ± 6 (10)
AVN	90 ± 5 (10)	86 ± 5 (10)	89 ± 5 (10)
HP	38 ± 1 (10)	34 ± 1 (10)	37 ± 2 (10)
VEN	103 ± 5 (10)	93 ± 4 (10)	97 ± 5 (10)
MAP	101 ± 3 (9)	104 ± 6 (10)	102 ± 3 (9)

HR = spontaneous heart rate; AVN, HP, VEN = AV nodal, His-Purkinje, and ventricular conduction time; MAP = mean femoral arterial pressure (mmHg).

rial pressure; VER = 20–40 msec increase in the P-R interval of the surface ECG, lead II. Experiments with NIF, as well as the preparation of NIF for intravenous administration and handling of plasma samples, were carried out under gold fluorescent lighting (Sylvania® Gold F40/GO) to minimize photodegradation of NIF.

Samples for plasma drug levels were taken from the femoral artery. Blood was put in heparinized tubes (B-D®) and centrifuged at 7000 rpm for 10 min. Plasma was drawn off into plastic transport tubes, and stored at −20° C until analyzed (by 6 weeks). Assays for plasma level of DIL, NIF, and VER were performed by Pharmacology and Toxicology Research Laboratories, Lexington, KY. Gas-liquid chromatography was used for NIF.[10] High-performance liquid chromatography was used for DIL and VER.[11,12] The linearity range for NIF was 1.0–1000 Ng/ml and coefficient of variation 3.0–8%. The linearity range for both DIL and VER was 10–1000 Ng/ml. The coefficient of variation for DIL was 2.0–12%, and for VER 2.0–10%.

In separate experiments in conscious dogs (N = 5), we determined the effect of time on plasma levels of DIL, NIF, and VER. These drugs were administered exactly as during experiments with anesthetics and calcium channel blockers, and samples were obtained 25–35, 75–85, and 105–115 min during dosing with calcium channel blockers. These time periods were the same ones as had been used for data collection during primary experiments.

Blood Gas and Electrolyte Determinations

Heparinized arterial samples were stored on ice and analyzed within 2 h of experiments for *p*H, P_{CO_2}, P_{O_2}, base excess (Corning® 178 *p*H/Blood Gas Analyzer), and ionized calcium (NOVA® 2 Biomedical Ionized Calcium Analyzer). Separate samples of arterial blood (non-heparinized) were centrifuded at 7000 rpm for 10 min and the serum analyzed for potassium and sodium (Beckman® Klina Flame).

Data Analysis and Statistical Methods

Values used for blood pressure and electrophysiologic data were always the average of four determinations. All data are reported as mean ± SEM. For each anesthetic sequence (fig. 2), overall significance was determined using Friedman's Rank Sum Test.[13] Nonparametric statistical methods were used throughout. Individual pairwise comparisons within sequences with an overall P value of <0.05 were analyzed using the paired Wilcoxon test.[14] Data for AV nodal conduction time were also tested for interactions (synergism) between the anesthetics and calcium channel blockers. Once again Friedman's Rank Sum Test was used for tests of overall significance. Sequences with an overall significance of $P < .05$ were analyzed using the paired Wilcoxon test.

Results

Arterial Blood Gas and Electrolyte Values

In conscious dogs, with or without calcium channel blockers or vehicle, ranges of values for blood gases, electrolytes, and plasma ionized Ca were: *p*H = 7.38–7.41, Pa_{CO_2} = 33–42 mmHg, Pa_{O_2} = 99–116 mmHg, K^+ = 4.3–5.0 mEq/l, Na^+ = 145–148 mEq/l, and Ca^{2+} = 2.33–2.65 mEq/l. In anesthetized dogs, values were: *p*H = 7.28–7.35, Pa_{CO_2} = 40–51 mmHg, Pa_{O_2} = 327–516 mmHg, K^+ = 4.0–4.5 mEq/l, Na^+ = 144–149 mEq/l, and Ca^{2+} = 2.35–2.73 mEq/l. While arterial *p*H and serum K^+ were lower, and Pa_{CO_2} and Pa_{O_2} higher, in anesthetized compared to conscious dogs ($P < 0.05$), there was no independent effect of anesthetic level, calcium channel blockers, or vehicle on blood gas, electrolyte, or plasma Ca^{2+} values.

Anesthetic Effects

Conscious (control) values for heart rate, specialized atrioventricular (A-V) conduction times, and mean femoral arterial pressure are listed in table 1 for each anesthetic group. Significant increases or decreases from these values produced by anesthesia without calcium channel blockers are shown in table 2. Spontaneous heart rate was unaffected by any anesthetic agent. AV nodal conduction time (AH) was prolonged by both levels of halothane. Prolongation of AH by 1.2 MAC enflurane (15.4 ± 4.7 msec, 10 dogs) and 1.6 MAC isoflurane (7.9 ± 4.7 msec, 11 dogs) was borderline sig-

nificant ($P = .058$ and .086, respectively). All anesthetics increased His-Purkinje conduction time (HP), with the greatest and comparable prolongation caused by enflurane and halothane. Isoflurane caused the largest decrease in mean arterial pressure (MAP) compared to awake. Comparable but smaller decreases in MAP were observed with enflurane and halothane. Except for 1 msec added prolongation of HP conduction by MAC 1.6 compared to 1.2 enflurane, increased level of anesthesia had no significant effects on any of the experimental variables.

Anesthetics and Calcium Channel Blockers

In table 3 are listed the conscious values for heart rate, specialized A-V conduction times, and mean femoral arterial pressure following the addition of the calcium channel blockers (CCB), diltiazem (DIL), nifedipine (NIF), vehicle (VEH) for NIF and verapamil (VER). Increases or decreases from control (awake without CCB) produced by the CCBs or CCBs with anesthesia are discussed below for each of the anesthetics.

Enflurane (table 4). Only DIL affected HR in awake dogs. AV nodal conduction time was increased in awake dogs by both DIL and VER. Heart rate compared to awake without CCB was unaffected by the CCB or CCB with enflurane. Prolongation of AH during anesthesia was greatest with VER. Three of ten dogs at each level of anesthesia developed complete heart block or AV junctional escape rhythm. Two additional dogs with VER were not studied at MAC 1.6 because MAP was less than 40 mmHg. Prolongation of AH by VER with 1.6 MAC ENF (58.6 ± 9.9 msec, five dogs) was borderline significant ($P = .059$). The increase in AH produced by DIL at both levels of enflurane was synergistic ($P < .05$). Neither DIL nor VER had additive effects to those of anesthesia on HP or VENT. Both DIL and VER acted synergistically with enflurane to reduce MAP ($P < .05$). Finally, most significant effects of NIF or its VEH on HR, specialized conduction times, or MAP were similar in both magnitude and direction.

Halothane (table 5). Prolongation of AH by DIL and VER during anesthesia was additive and greatest with VER. One of ten dogs with VER developed complete heart block at each level of anesthesia. Two of ten dogs with VER developed type I, 2° AV (Wenckebach) block at 1.6 MAC halothane, and one of ten did so at the 1.2 MAC level. Neither DIL nor VER had additive effects to those of halothane on any of the experimental variables. There were no significant effects of the CCBs on MAP; nor were there significant interactions affecting MAP between halothane and the CCBs.

TABLE 2. Significant Effects of Enflurane, halothane, or Isoflurane on Spontaneous Heart Rate, Specialized Atrioventricular Conduction Times, and Arterial Pressure. Increases (+) or Decreases (−) Shown as Mean ± SEM. Number of Dogs Shown in Parentheses

	Awake *Versus* MAC 1.2	Awake *Versus* MAC 1.6	MAC 1.2 *Versus* 1.6
Enflurane			
HR	NS	NS	NS
AVN	NS	NS	NS
HP	3.9 ± .7 (10)	4.8 ± .7 (10)	.9 ± .3 (10)
VEN	9.4 ± 1.9 (10)	10.3 ± 2.2 (10)	NS
MAP	−28.0 ± 4.4 (9)	−33.2 ± 3.9 (9)	NS
Halothane			
HR	NS	NS	NS
AVN	19.5 ± 3.6 (10)	24.0 ± 4.3 (10)	NS
HP	3.5 ± .5 (10)	3.3 ± .4 (10)	NS
VEN	9.0 ± .9 (10)	9.6 ± 1.1 (10)	NS
MAP	−28.3 ± 7.6 (9)	−33.3 ± 6.3 (10)	NS
Isoflurane			
HR	NS	NS	NS
AVN	NS	NS	NS
HP	3.3 ± .6 (10)	3.7 ± .6 (10)	NS
VEN	4.0 ± 1.5 (10)	5.4 ± .9 (10)	NS
MAP	−35.2 ± 4.7 (9)	−42.3 ± 3.5 (9)	NS

Abbreviations are as in table 1.

Isoflurane (table 6). Prolongation of AH by DIL and VER with isoflurane was both comparable and additive. One of 11 dogs with VER developed complete heart block at each level of isoflurane. Type I, 2° AV (Wenckebach) block was observed in one dog with VER at the 1.2 MAC level. There were no added effects of

TABLE 3. Spontaneous Heart Rate, Specialized Atrioventricular Conduction Times and Mean Arterial Pressure in Awake Dogs with Diltiazem, Nifedipine, Vehicle for Nifedipine, or Verapamil. All Values are Mean ± SEM with the Number of Dogs Shown in Parentheses.

	Diltiazem	Nifedipine	Vehicle	Verapamil
Enflurane				
HR	123 ± 7 (8)	122 ± 6 (9)	112 ± 4 (9)	139 ± 8 (9)
AVN	99 ± 5 (8)	91 ± 6 (9)	90 ± 4 (9)	120 ± 9 (9)
HP	38 ± 1 (8)	38 ± 1 (9)	38 ± 1 (9)	38 ± 1 (9)
VEN	105 ± 5 (8)	102 ± 5 (9)	103 ± 5 (9)	100 ± 5 (9)
MAP	94 ± 3 (8)	96 ± 2 (9)	107 ± 6 (9)	97 ± 3 (10)
Halothane				
HR	121 ± 7 (8)	134 ± 10 (8)	107 ± 6 (9)	130 ± 8 (10)
AVN	117 ± 9 (8)	93 ± 7 (8)	97 ± 4 (9)	120 ± 8 (10)
HP	35 ± 1 (8)	35 ± 1 (8)	36 ± 1 (9)	36 ± 1 (10)
VEN	99 ± 4 (8)	98 ± 5 (8)	99 ± 4 (9)	97 ± 1 (10)
MAP	99 ± 4 (8)	100 ± 5 (8)	101 ± 3 (9)	95 ± 3 (10)
Isoflurane				
HR	113 ± 7 (9)	123 ± 8 (10)	113 ± 7 (10)	140 ± 5 (10)
AVN	116 ± 6 (8)	88 ± 4 (10)	98 ± 7 (10)	114 ± 6 (11)
HP	38 ± 2 (8)	39 ± 2 (10)	39 ± 2 (10)	38 ± 2 (11)
VEN	99 ± 6 (8)	101 ± 5 (10)	102 ± 5 (10)	102 ± 5 (11)
MAP	95 ± 6 (9)	100 ± 3 (10)	100 ± 4 (10)	100 ± 4 (9)

Abbreviations are as in table 1.

TABLE 4. Significant Effects of Diltiazem, Nifedipine, Vehicle for Nifedipine, or Verapamil on Spontaneous Heart Rate, Specialized Atrioventricular Conduction Times, and Arterial Pressure in Dogs Anesthetized with Enflurane. Increases (+) or Decreases (−) Shown as Mean ± SEM. Number of Dogs Shown in Parentheses

	A *Versus* AB	A *Versus* B1.2	A *Versus* B1.6	AB *Versus* B1.2	AB *Versus* B1.6	B1.2 *Versus* B1.6
Diltiazem						
HR	19 ± 3 (8)	NS	NS	−33 ± 7 (8)	−28 ± 7 (8)	NS
AVN	13 ± 2 (8)	48 ± 8 (8)	48 ± 8 (8)	34 ± 9 (8)	34 ± 8 (8)	NS
HP	1 ± 0 (8)	5 ± 0 (8)	4 ± 0 (8)	4 ± 0 (8)	3 ± 0 (8)	NS
VEN	NS	9 ± 1 (8)	9 ± 2 (8)	8 ± 1 (8)	8 ± 2 (8)	NS
MAP	−10 ± 2 (8)	−45 ± 3 (8)	−57 ± 3 (8)	−35 ± 3 (8)	−48 ± 3 (8)	−12 ± 2 (8)
Nifedipine						
HR	NS	NS	NS	NS	NS	NS
AVN	NS	22 ± 7 (9)	NS	20 ± 8 (9)	NS	NS
HP	1 ± 1 (9)	5 ± 0 (9)	6 ± 1 (9)	4 ± 1 (9)	4 ± 1 (9)	NS
VEN	2 ± 1 (9)	6 ± 1 (9)	8 ± 2 (9)	NS	6 ± 2 (9)	2 ± 1 (9)
MAP	NS	−40 ± 3 (9)	−48 ± 5 (9)	−38 ± 3 (9)	−46 ± 5 (9)	−8 ± 3 (9)
Vehicle						
HR	NS	NS	NS	NS	NS	NS
AVN	7 ± 3 (9)	20 ± 6 (9)	16 ± 4 (9)	12 ± 6 (9)	NS	NS
HP	NS	10 ± 6 (9)	6 ± 1 (9)	9 ± 6 (9)	5 ± 1 (9)	NS
VEN	5 ± 1 (9)	10 ± 2 (9)	13 ± 2 (9)	5 ± 2 (9)	8 ± 1 (9)	NS
MAP	NS	−38 ± 7 (9)	−40 ± 9 (9)	−36 ± 8 (9)	−38 ± 9 (9)	NS
Verapamil						
HR	NS	NS	NS	−46 ± 8 (6)	NS	NS
AVN	32 ± 5 (9)	66 ± 11 (7)	NS	NS	NS	NS
HP	1 ± 0 (9)	5 ± 1 (7)	NS	4 ± 1 (6)	NS	NS
VEN	NS	9 ± 2 (7)	NS	8 ± 2 (6)	NS	NS
MAP	−7 ± 2 (9)	−57 ± 4 (7)	NS	−47 ± 4 (6)	NS	NS

A = awake; AB = awake with calcium channel blocker (CCB); B1.2 = enflurane 1.2 MAC with CCB; B1.6 = Enflurane 1.6 MAC with CCB. Other abbreviations as in Table 1.

TABLE 5. Significant Effects of Diltiazem, Nifedipine, Vehicle for Nifedipine, or Verapamil on Spontaneous Heart Rate, Specialized Atrioventricular Conduction Times, and Arterial Pressure in Dogs Anesthetized with Halothane. Increases (+) or Decreases (−) Shown as Mean ± SEM. Number of Dogs Shown in Parentheses

	A *Versus* AB	A *Versus* B1.2	A *Versus* B1.6	AB *Versus* B1.2	AB *Versus* B1.6	B1.2 *Versus* B1.6
Diltiazem						
HR	NS	NS	NS	NS	NS	NS
AVN	19 ± 4 (7)	30 ± 7 (8)	38 ± 10 (8)	NS	NS	NS
HP	NS	5 ± 1 (8)	6 ± 1 (8)	4 ± 1 (8)	5 ± 1 (7)	NS
VEN	NS	10 ± 2 (8)	12 ± 2 (8)	7 ± 2 (7)	8 ± 3 (7)	NS
MAP	NS	−34 ± 7 (7)	−41 ± 5 (8)	NS	−35 ± 5 (7)	−8 ± 4 (7)
Nifedipine						
HR	NS	NS	NS	NS	−16 ± 4 (8)	NS
AVN	NS	16 ± 6 (8)	17 ± 5 (8)	NS	18 ± 7 (8)	NS
HP	NS	4 ± 1 (8)	5 ± 1 (8)	3 ± 1 (8)	4 ± 1 (8)	NS
VEN	NS	10 ± 2 (8)	11 ± 2 (8)	7 ± 2 (8)	9 ± 2 (8)	NS
MAP	NS	−27 ± 6 (8)	−41 ± 4 (8)	−22 ± 4 (8)	−35 ± 4 (8)	NS
Vehicle						
HR	NS	NS	NS	NS	NS	NS
AVN	NS	27 ± 6 (9)	NS	21 ± 6 (9)	NS	−11 ± 4 (9)
HP	2 ± 0 (9)	6 ± 1 (9)	6 ± 1 (9)	4 ± 1 (9)	4 ± 1 (9)	NS
VEN	3 ± 0 (9)	12 ± 1 (9)	13 ± 1 (9)	9 ± 1 (9)	9 ± 1 (9)	NS
MAP	NS	−37 ± 4 (9)	−44 ± 5 (9)	−31 ± 4 (9)	−38 ± 5 (9)	NS
Verapamil						
HR	NS	NS	NS	NS	NS	NS
AVN	27 ± 3 (9)	56 ± 10 (9)	49 ± 6 (8)	33 ± 12 (8)	NS	NS
HP	NS	5 ± 1 (9)	6 ± 1 (8)	4 ± 1 (8)	5 ± 1 (7)	NS
VEN	NS	9 ± 1 (9)	10 ± 2 (8)	8 ± 1 (8)	8 ± 3 (7)	NS
MAP	NS	−39 ± 4 (9)	−40 ± 5 (8)	−29 ± 4 (7)	−31 ± 2 (6)	NS

Abbreviations are as in tables 1 and 4.

TABLE 6. Significant Effects of Diltiazem, Nifedipine, Vehicle for Nifedipine, or Verapamil on Spontaneous Heart Rate, Specialized Atrioventricular Conduction Times, and Arterial Pressure in Dogs Anesthetized with Isoflurane. Increases (+) or Decreases (−) Shown as Mean ± SEM. Number of Dogs Shown in Parentheses

	A versus AB	A versus B1.2	A versus B1.6	AB versus B1.2	AB versus B1.6	B1.2 versus 1.6
Diltiazem						
HR	NS	NS	NS	NS	NS	NS
AVN	18 ± 3 (7)	35 ± 6 (8)	35 ± 8 (8)	NS	NS	NS
HP	NS	4 ± 1 (8)	5 ± 1 (8)	3 ± 1 (7)	4 ± 1 (7)	NS
VEN	NS	12 ± 4 (8)	14 ± 5 (8)	5 ± 1 (7)	7 ± 2 (7)	NS
MAP	NS	−40 ± 6 (8)	−44 ± 5 (8)	−34 ± 4 (7)	−36 ± 4 (7)	NS
Nifedipine						
HR	NS	NS	NS	NS	NS	NS
AVN	NS	NS	NS	NS	NS	NS
HP	1 ± 1 (10)	5 ± 1 (10)	6 ± 1 ( )	3 ± 1 (10)	4 ± 1 (10)	NS
VEN	NS	11 ± 3 (10)	12 ± 3 (10)	5 ± 2 (10)	6 ± 2 (10)	NS
MAP	−6 ± 2 (10)	−40 ± 6 (10)	−43 ± 5 (10)	−33 ± 7 (10)	−36 ± 6 (10)	NS
Vehicle						
HR	NS	12 ± 5 (10)	9 ± 4 (10)	NS	NS	NS
AVN	NS	NS	NS	NS	NS	NS
HP	2 ± 0 (10)	6 ± 1 (10)	6 ± 1 (10)	4 ± 1 (10)	4 ± 1 (10)	NS
VEN	6 ± 3 (10)	12 ± 3 (10)	13 ± 3 (10)	7 ± 1 (10)	7 ± 2 (10)	NS
MAP	NS	−38 ± 4 (9)	−47 ± 5 (9)	−35 ± 4 (9)	−44 ± 6 (9)	NS
Verapamil						
HR	34 ± 6 (11)	NS	NS	−38 ± 7 (10)	−43 ± 8 (10)	NS
AVN	25 ± 4 (11)	41 ± 8 (10)	43 ± 12 (10)	16 ± 7 (10)	NS	NS
HP	NS	4 ± 1 (10)	4 ± 1 (10)	4 ± 1 (10)	4 ± 1 (10)	NS
VEN	NS	10 ± 3 (10)	10 ± 4 (10)	6 ± 1 (10)	6 ± 1 (10)	NS
MAP	NS	−38 ± 4 (9)	−51 ± 3 (9)	−35 ± 4 (9)	49 ± 5 (9)	NS

Abbreviations are as in tables 1 and 4.

any CCB on HP and VENT during isoflurane. Finally, there were no additive or synergistic effects of the CCBs to those of isoflurane which affected MAP.

PLASMA DRUG LEVELS

Plasma levels for DIL, NIF, and VER remained fairly constant over time in conscious dogs. Values at the 25–35-, 75–85-, and 105–115-min time periods after dosing with DIL were 142 ± 4, 158 ± 13, and 186 ± 27 ng/ml, respectively. For NIF, they were 6 ± 2, 5 ± 2, and 4 ± 1 ng/ml, respectively. For VER they were 147 ± 13, 138 ± 24, and 177 ± 28 ng/ml, respectively. Plasma levels of DIL and VER were increased by all anesthetics (table 7), while those of NIF were not affected by any of the anesthetics. Some plasma samples for NIF were discarded consequent to inadvertent exposure to light.

Discussion

SPECIALIZED AV CONDUCTION

The observed increases in specialized AV conduction times over conscious control values with enflurane and halothane—AV nodal (17–28%), His-Purkinje (9–13%), and ventricular (9–10%)—are comparable to those noted in our previous study in dogs.[1] The present data, which indicate little effect of 1.2 or 1.6 MAC isoflurane on AV nodal conduction time and 4–10% prolongation of His-Purkinje and ventricular specialized

TABLE 7. Plasma Levels (ng/ml) of Diltiazem, Nifedipine, or Verapamil in Awake Dogs, and Increase in Plasma Level with Enflurane, Halothane, or Isoflurane (Number of Dogs Shown in Parentheses)

	AB	AB *Versus* B1.2	AB *Versus* B1.6	B1.2 *Versus* B1.6
Enflurane				
Diltiazem	109 ± 11 (7)	89 ± 24 (7)	97 ± 20 (7)	NS
Nifedipine	4 ± 1 (4)	NS	NS	NS
Verapamil	147 ± 9 (9)	NS	115 ± 31 (8)	NS
Halothane				
Diltiazem	94 ± 13 (6)	82 ± 13 (7)	87 ± 9 (7)	NS
Nifedipine	7 ± 2 (6)	NS	NS	NS
Verapamil	215 ± 39 (10)	69 ± 12 (8)	99 ± 27 (7)	NS
Isoflurane				
Diltiazem	124 ± 9 (10)	82 ± 14 (8)	125 ± 18 (8)	NS
Nifedipine	4 ± 1 (3)	NS	NS	NS
Verapamil	201 ± 30 (8)	76 ± 18 (10)	77 ± 28 (8)	NS

AB = plasma levels in awake dogs; other abbreviations are as in table 1 and 4.

conduction times, are also in agreement with our earlier findings for isoflurane.[1]

Both diltiazem and verapamil increased AV nodal conduction time in conscious dogs, consistent with their reported electrophysiologic actions.[2] Prolongation of conduction with verapamil in awake dogs was greater (ranged from 28 to 38% in the three test groups) than with diltiazem (range 15–23%). However, neither diltiazem or verapamil affected infranodal (His-Purkinje, ventricular) conduction times in awake dogs. Nor did these drugs have additive effects to those of the anesthetics on infranodal conduction.

While verapamil and diltiazem had little effect on infranodal conduction time in anesthetized dogs, there was pronounced additive (halothane, isoflurane) or synergistic (enflurane) prolongation of AV nodal conduction time by diltiazem. There was additive prolongation of AV nodal conduction time by verapamil with each of the anesthetic agents. Verapamil, particularly with enflurane, caused the greatest impairment of conduction in anesthetized dogs. Three dogs had complete heart block or AV junctional escape rhythm with verapamil at each level of enflurane. At least one dog had type I, 2° (Wenckebach), or complete heart block at each level of anesthesia with halothane or isoflurane in dogs blocked with verapamil. In dogs with intact AV nodal conduction, prolongation of conduction time (compared to awake without verapamil) ranged from 46% (1.2 MAC isoflurane) to 69% (1.6 MAC enflurane). In contrast to these findings for verapamil, no dogs had heart block with diltiazem and any anesthetic, in agreement with the findings of Kapur *et al.* for enflurane,[6] halothane,[15] and isoflurane[7] for plasma diltiazem levels < 300 ng/ml. Added prolongation of AV nodal conduction time by the addition of anesthetics to dogs blocked with diltiazem ranged from 36% (1.6 MAC halothane) to 55% (both levels of enflurane). Added impairment of AV nodal conduction by anesthetics in dogs blocked with verapamil or diltiazem is not surprising, since the anesthetics and calcium channel blockers act similarly to interfere with calcium ion flux across excitable membranes.[16–19] Furthermore, all anesthetics increased the plasma levels of diltiazem and verapamil (more discussion, below). In conscious dogs, there appears to be good correlation between plasma level of diltiazem[20] or verapamil[21] and prolongation of the P-R interval of the surface electrocardiogram. Consequently, further impairment of AV nodal conduction by anesthesia in dogs with diltiazem is possibly due both to similar actions of the anesthetics and calcium channel blockers at the AV node and to an increase in plasma level of diltiazem or verapamil with anesthesia.

Nifedipine had no apparent effect on AV nodal conduction time in awake or anesthetized dogs. However, there was small prolongation of AV nodal conduction time by the vehicle for nifedipine (15% polyethylene glycol, 15% ethanol) in some animals. We speculate that any direct action of nifedipine, or vehicle in the presence of nifedipine, to prolong AV nodal conduction time was opposed by increased sympathetic tone in response to vasodilation with nifedipine.[3] We are unaware of published reports for the effect of vehicle or its components (ethanol, polyethylene glycol) on specialized AV conduction times. Finally, with nifedipine, both it and its vehicle caused prolongation of infranodal specialized conduction in awake, but not anesthetized, dogs. Prolongation of conduction was similar with both nifedipine and vehicle, suggesting that vehicle was responsible for any increase in infranodal conduction time with nifedipine. Nifedipine alone is not associated with local anesthetic (fast-channel blocking) activity.[16] Hence, nifedipine would not be expected to impair infranodal nodal conduction.

Anesthetics and Channel Blocker Plasma Levels

Diltiazem and verapamil levels were increased during each of the anesthetics, but there was no added effect of increased anesthetic level to increase the plasma level of diltiazem or verapamil. There was no effect of any anesthetic on plasma nifedipine levels. That the increase in plasma level of diltiazem and verapamil is due to the effects of the anesthetic is supported by our data for plasma drug levels in conscious dogs. There were no differences between plasma drug levels sampled at the 25–35-, 75–85-, and 105–115-min time periods in conscious dogs, although plasma drug levels tended to be higher at the last time period. These sampling time periods corresponded to time periods during study when electrophysiologic testing was performed. Chelly *et al.*[4] and Rogers *et al.*[5] have also observed increased plasma levels of verapamil in dogs anesthetized with enflurane, halothane, or isoflurane. A later pharmacokinetic study of the interaction between anesthetics was performed by this same group of investigators.[22] Their data suggest that increased plasma levels of verapamil noted early during anesthesia in our dogs (75–85 min) could have resulted from decreased central to peripheral intercompartmental clearance. There appear to be no comparable pharmacokinetic data for diltiazem in dogs anesthetized with any of the volatile anesthetics. Increased levels at the later time period (105–115 min) may have more been due to a reduction in hepatic

blood flow with the anesthetics.[23,24] Both diltiazem and verapamil appear to have high hepatic extraction ratios,[25] and systemic clearance of verapamil has been shown to be dependent on liver blood flow.[26]

Implications for Clinical Management

Because of species differences, our findings in dogs should be applied with caution to humans. Nevertheless, the dog is probably the most widely used *in vivo* model for human cardiac electrophysiology. While all anesthetics caused added prolongation of AV nodal conduction time in dogs with plasma levels of diltiazem or verapamil that are likely to be effective against reentrant supraventricular tachyarrhythmias,[2] impairment of conduction—as evidenced by complete heart block and AV junctional rhythms—was greatest with enflurane administered to dogs receiving verapamil. We hasten to point out that the increase in plasma levels of diltiazem or verpamil, the likely mechanism for added prolongation of conduction or heart block, was observed during intravenous (acute) administration of these drugs. There are no data indicating significant pharmacokinetic interactions affecting the plasma level of diltiazem or verapamil following oral (chronic) dosing. Merin *et al.* did not report heart block in dogs receiving enflurane, halothane, or isoflurane after chronic oral dosing for at least 2 weeks with verapamil.[27] This was in contrast to earlier studies with intravenous verapamil and halothane[4] or enflurane and isoflurane,[5] where heart block was observed with anesthesia and verapamil plasma levels similar to ours. Regardless, we have observed heart block in patients receiving oral verapamil or diltiazem, who may also have been on beta adrenergic blocking drugs, and who were then anesthetized with a potent inhalation anesthetic (unpublished observations). Thus, until there are studies of the cardiac electrophysiologic effects of the potent inhalation anesthetics and orally administered diltiazem or verapamil, it would seem prudent to be alert to the potential for additive or synergistic effects on AV nodal conduction, with the possibility for heart block.

This study did not address the issue of clinical management of heart block resulting from the interaction of the potent volatile anesthetics with the calcium channel blockers. Prolongation of conduction was greatest at the AV node, which is richly innervated by the autonomic nervous system (in contrast to the infranodal conduction system). Thus, it is likely that most hemodynamically deleterious AV conduction block or AV junctional escape rhythms with the anesthetics and diltiazem or verapamil could be managed by pharmacologic means, *e.g.*, beta-adrenergic agonists or antimuscarinics agents. Additional measures might involve substituting a more balanced anesthetic technique, removing the potent inhalation anesthetic, or lessening of the anesthetic concentration. However, removing the inhalation anesthetic might be preferred, since both the anesthetics and calcium channel blockers exert similar (calcium antagonistic) and additive or synergistic (consequent to adverse pharmacokinetic action) prolongation of AV nodal conduction. Finally, for hemodynamically significant block not easily reversed by pharmacologic means or by removing the offending anesthetic agent, temporary pacing should be considered.

The authors wish to thank David Redon and Tamara Yeager for technical assistance, Sherrie Emoto and Jan Feyzi of the Biostatistics Center for statistical assistance, Fern Reilly and Pamela Licht for preparation of the manuscript, and Ben F. Rusy, M.D., for consultations during all phases of this investigation.

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