Comparison of Cardiovascular Responses to Verapamil during Enflurane, Isoflurane, or Halothane Anesthesia in the Dog

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The cardiovascular responses to increasing infusion rates of the slow calcium channel inhibitor, verapamil, were studied in three groups of dogs during either enflurane, isoflurane, or halothane anesthesia. Control hemodynamic values and plasma samples were taken after 2 h of anesthesia with the given agent. Increasing infusion rates of verapamil were given to achieve a range of plasma verapamil levels up to approximately 500 ng·ml^{-1}. Each infusion rate was administered for 30 min, at which time repeat measurements and plasma samples for verapamil were taken. Mean arterial blood pressure, cardiac index, and left ventricular dP/dt decreased with increasing plasma verapamil levels in the enflurane and isoflurane groups compared with the control values. The values for the enflurane–verapamil combination were significantly lower than those for the other anesthetics at comparable verapamil levels. Compared with enflurane, higher verapamil levels were required with isoflurane to achieve the equivalent degree of hemodynamic depression. A higher incidence of conduction abnormalities also was noted in the enflurane group. In the halothane group, the only significant change observed at these verapamil levels, achieved by continuous infusion, was a prolongation of the PR interval of the ECG. In this animal model, verapamil was least well tolerated by the cardiovascular system during enflurane anesthesia. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: anesthetics; myocardial function. Ions: calcium. Pharmacology: verapamil.

VERAPAMIL, a member of the class of slow-channel inhibiting drugs that interfere with the calcium-dependent slow currents across excitable cell membranes, now is in clinical use as an antiarrhythmic agent for the treatment of supraventricular re-entrant arrhythmias or to slow the ventricular rate in atrial fibrillation and atrial flutter and is also used for the relief of classical and variant angina pectoris.

The interactions of verapamil with volatile anesthetics are the subject of current investigation in a number of laboratories. We have shown transient depression of systemic vascular resistance and myocardial contractility after rapid bolus administration of 0.2 mg/kg verapamil during 1.1 MAC halothane anesthesia in the dog.[1] The time course of these effects suggested that the hemodynamic consequences of rapid verapamil administration correlated with plasma verapamil levels.[1,2]

In unanesthetized patients undergoing cardiac catheterization, Chew and colleagues noted a correlation of the severity of verapamil-associated myocardial depression with the degree of left ventricular dysfunction present before verapamil administration.[3] In thiopental-anesthetized dogs, significant hemodynamic changes were observed only with high plasma verapamil levels (>200 ng/ml).[4] In a canine right heart bypass model for the evaluation of interactions of verapamil with isoflurane, significant myocardial depression was observed at relatively low plasma verapamil levels (<80 ng/ml).[5] Since the usual clinical anesthetic situation is that of an intact subject, with the addition of other agents to thiopental, this study was undertaken to investigate changes in cardiovascular function over a range of plasma verapamil levels during steady state inhalation anesthesia with enflurane, isoflurane, or halothane in the intact dog to determine if any difference could be detected in the physiologic response of the cardiovascular system to verapamil depending upon the anesthetic agent present.

Methods

Mongrel dogs of either sex weighing 19.6 ± 0.6 kg (mean ± SE) were anesthetized with 20 mg/kg thiopental intravenously followed by either enflurane (n = 9), isoflurane (n = 7), or halothane (n = 7) in oxygen anesthesia at concentrations approximating 1 MAC. MAC in the dog has been estimated at 0.87% for halothane,[6] 2.27% for enflurane,[7] and 1.48% for isoflurane.[8] The trachea was intubated and ventilation was controlled to maintain end-tidal P_{CO_2} between 35–40 mmHg as measured continuously by a Beckman® LB-3 infrared CO_2 analyzer and corroborated by intermittent arterial blood samples analyzed by a Corning® Blood Gas Analyzer Model 165. Esophageal temperature was maintained between 37° C and 39° C with a warming blanket and a heat lamp.

Isotonic crystalloid infusion at a rate of 5 ml·kg^{-1}·h^{-1} and drugs were given via a femoral venous cannula. Direct arterial pressure measurements and blood for plasma drug levels were obtained from a femoral arterial cannula. A balloon-tipped flow-directed catheter was positioned in a pulmonary artery via the right external jugular vein. Thermodilution cardiac outputs (CO) intermittently were measured using a Santa Barbara Technology cardiac output computer model 1700 and values taken as the mean of the three consecutive measurements. A micromanometer-tipped catheter (Millar Instruments, Inc.) was positioned in the left ventricle via the left carotid artery.

Limb lead II of the electrocardiogram (ECG), heart rate (HR), phasic and mean arterial blood pressure (MAP), left ventricular pressure, electrically derived left ventricular dP/dt (LV dP/dt), and end-tidal CO_2 concentration were recorded continuously on a Hewlett–Packard® oscillograph, model 7758B, with intermittent recordings of the ECG at high paper speed (100 mm/s) on a Grass® model 79 polygraph. A DEC® MINC-11® computer was used for on-line data analysis and calculation of systemic vascular resistance index (SVRI) and cardiac index (CI). Blood anesthetic levels were measured every 30 min by gas chromatography.[9,10] Plasma verapamil levels were measured by high-performance liquid chromatography.[11]

After a 2-h stabilization period on a given inhalation anesthetic, control measurements and plasma samples were taken. A loading dose of 0.5 mg verapamil was given over 30 s followed by increasing infusion rates (1.25, 2.5, 3.75, 5.0, etc., $\mu g \cdot kg^{-1} \cdot min^{-1}$) of verapamil for 30 min each, at which time repeat measurements were taken. Plasma verapamil samples were taken in most animals at 15, 25, and 30 min after starting each infusion, though some animals only had samples taken at 25 and 30 min. Pilot studies had indicated that verapamil plasma levels at that time (25 and 30 min) already had plateaued (table 1) after only increasing the infusion rate by the small increments indicated in the infusion protocol, thus no additional boluses of verapamil were given and values are reported as a function of plasma verapamil levels. No further verapamil was given if mean arterial pressure fell below 50 mmHg.

Analysis of variance for repeated measures with Bonferroni t test was used to compare progressive changes within one anesthetic group. Analysis of variance with a weighted t test was used to evaluate differences between the anesthetic groups. The technique of linear regression with the calculation of correlation coefficients was used to evaluate the relationship between two variables. Statistical significance was assumed when the P value was less than 0.05.

Results

Blood anesthetic levels of 2.12% ± 0.02% enflurane (nine dogs), 1.34% ± 0.1% isoflurane (seven dogs), and 0.93% ± 0.01% halothane (seven dogs), were maintained during these experiments. All data are presented as a function of verapamil plasma level rather than infusion rate. The arithmetically increasing infusion rate schedule for verapamil used in this study resulted in a wide range of plasma verapamil levels from a low of 29 ng/ml to a high of 1,060 ng/ml, with overlapping levels among the various infusion rates, attributable to individual variation in drug disposition among the animals. As seen in table 1, there was no statistically significant difference between the mean plasma verapamil levels at 25 compared with 30 min of each drug infusion rate, indicating a relatively steady state at the point of measurement. The decrease

TABLE 1. Plasma Verapamil Concentrations after 25 and 30 Minutes of Continuous Infusion

Infusion Rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	n	Verapamil Level* ($ng \cdot ml^{-1}$)	
		25 min	30 min
1.25	16	96 ± 10	99 ± 11
2.50	18	98 ± 8	103 ± 11
3.75	17	159 ± 13	151 ± 13
5.00	16	226 ± 24	220 ± 16
6.25	16	290 ± 22	319 ± 26
7.50	12	400 ± 45	398 ± 66
8.75	12	436 ± 52	433 ± 51
10.00	10	392 ± 44	387 ± 40

* Mean ± SE; no significant difference between 25 and 30 min values for any infusion rate.

in number of samples with increasing infusion rate and the leveling off of the mean levels at higher infusion rates resulted because no further verapamil was given as higher plasma levels in the animals resulted in arterial pressures below 50 mmHg.

Mean values for HR, MAP, LV dP/dt, CI, SVRI, and PR interval of the ECG are plotted as a function of verapamil level in figure 1. The three groups had equivalent control values for MAP, HR, SVR, and PR interval of the ECG ($P > 0.05$). There was a significant difference among the three groups in control LV dP/dt, with values in descending order from isoflurane to halothane to enflurane. Isoflurane control CI was significantly greater than that of enflurane.

MAP, LV dP/dt, and CI all decreased with increasing plasma verapamil level during isoflurane or enflurane anesthesia in our model. Values observed during enflurane were significantly less than those during halothane or isoflurane anesthesia. The percentage of MAP values less than 70 mmHg is plotted as a function of verapamil level in figure 2. The enflurane animals showed a progressive increase in low MAP values as verapamil levels rose. MAP values less than 70 mmHg were not observed with isoflurane until verapamil values rose above 400 ng/ml. No values below 70 mmHg were observed in the halothane group. SVRI was not statistically different from control after 30 min of a constant infusion of verapamil in these animals with any of the anesthetics.

Decreases in heart rate were only significant in the enflurane group. The number of animals demonstrating conduction abnormalities (second- or third-degree heart block, sinus arrest) at plasma verapamil levels less than 525 ng/ml were distributed as follows: enflurane group 5/9 dogs, isoflurane group 1/7 dogs, halothane group 2/7 dogs. Above a verapamil level of 400 $ng \cdot ml^{-1}$, only one of nine enflurane animals still had both a MAP greater than 50 mmHg and a sinus rhythm.

Discussion

This study was stimulated by the work of Mangiardi *et al.* who were unable to demonstrate significant changes
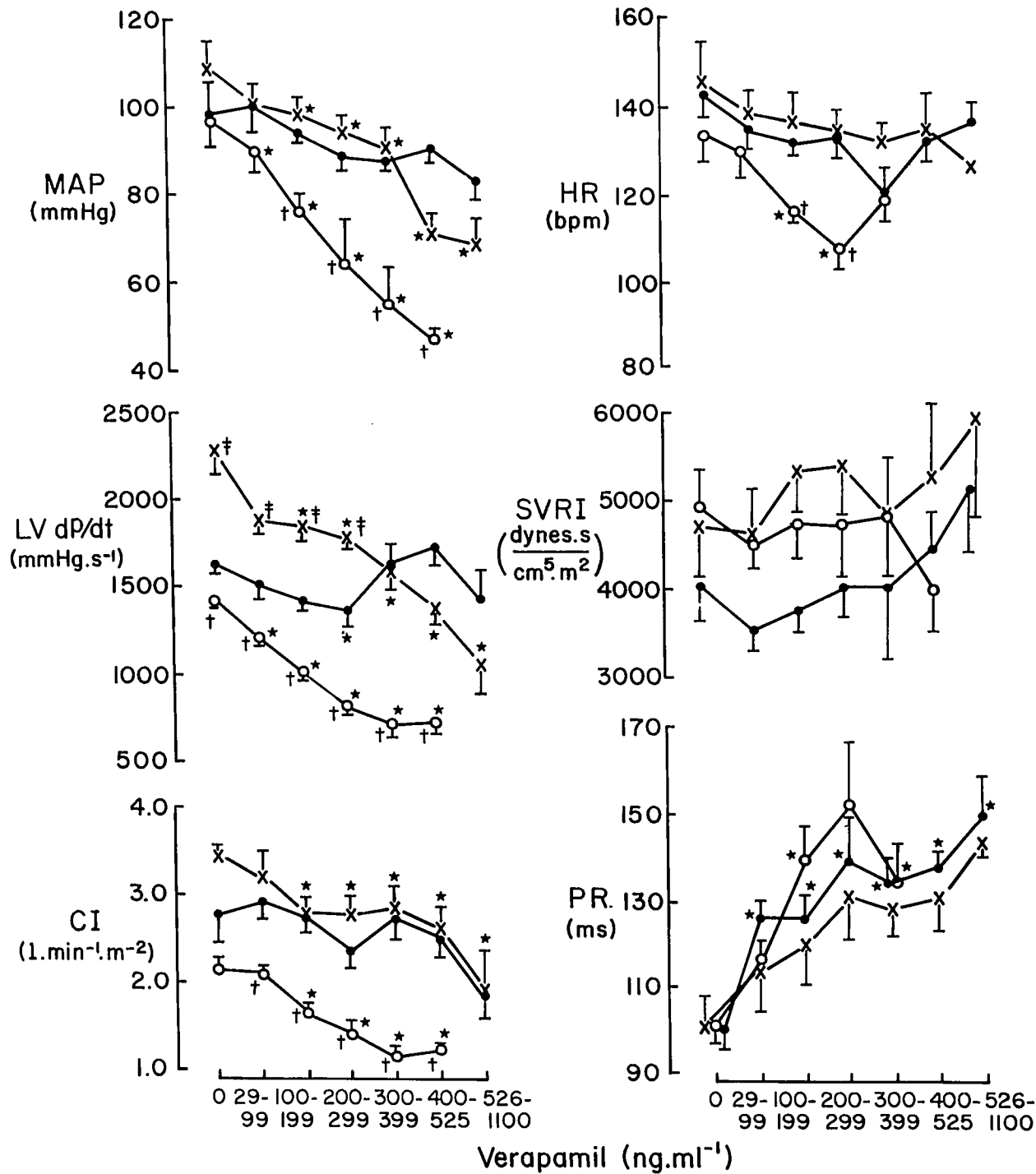
FIG. 1. Cardiovascular values (mean ± SE) as a function of plasma verapamil level for animals anesthetized with enflurane (n = 9; O——O); isoflurane (n = 7; X——X); or halothane (n = 7; ●——●). Values for n given below = number of measurements at each verapamil level for each anesthetic group. Note no values for enflurane above 525 ng/ml verapamil. No values for enflurane HR and PR interval above 400 ng/ml because of second-degree or third-degree heart block. * = $P < 0.05$ compared with control; † = $P < 0.05$ compared with both halothane and isoflurane; ‡ = $P < 0.05$ compared with halothane.

Values for n:

	Verapamil Levels (ng/ml)					
	29–99	100–199	200–299	300–399	400–525	526–1,100
Halothane	7	15	10	5	9	5
Isoflurane	10	15	12	9	10	5
Enflurane	14	15	7	8	3	—

in cardiovascular functions other than a slight decrease in blood pressure and prolongation of AV conduction in thiopental anesthetized dogs after verapamil unless verapamil levels rose above 200 ng/ml.[4] This was considered a favorable finding by those authors, since effective antiarrhythmic plasma verapamil levels are most likely at less than 150 ng/ml[12,13] and conduction effects may be present at quite low plasma levels.[2,14]

Studies by Lynch and co-workers indicate that inhalational anesthetics interfere with slow-channel function in a dose-dependent manner, however, enflurane concentrations above 2% were needed to influence the slow channel in their model.[15,16] Inhalation anesthetics do affect intracellular calcium homeostasis by multiple mechanisms, however, and thus it can be anticipated that plasma verapamil levels tolerated without cardiovascular changes in an unanesthetized subject may result in changes when given during inhalational anesthesia.

Though the steady state in the present experiments may include a minor contribution from residual thiopental, previous work with the anesthetic induction used here has shown that 2 h after thiopental administration, plasma thiopental levels are very low on the flat part of the elimination curve and change little with time.[2] Thus, the subsequent cardiovascular changes observed during steady states anesthesia reasonably can be attributed to verapamil administration.

Control values for the three anesthetics in this study were comparable for MAP, HR, CI, SVRI, and PR interval of the ECG, except for a significantly lower control CI in the enflurane group compared with the isoflurane group. These findings are similar to those of Horan et al.[17] and Merin,[18] who found little difference in these routinely measured parameters among halothane-, enflurane-, and isoflurane-anesthetized animals at concentrations of 1 MAC. Measurements of control LV dP/dt in our study showed differences among the three anesthetics, which may indicate that our anesthetic levels were not truly equipotent since we have only tested MAC in our animals for halothane (0.8 ± 0.04% blood level).[19] Merin[18] did not find very much difference in LV dP/dt among the anesthetics at 1 MAC, while Horan et al.[17] reported greater absolute values of LV dP/dt during isoflurane anesthesia. In addition, MAC levels have been reported in the literature as end-tidal concentrations, while blood anesthetic levels reported by our laboratory are lower than corresponding end-tidal levels (measured by a Perkin–Elmer mass spectrometer model MGA-1100), with the following regression equation: [halothane]$_{end\,tidal}$ = 0.63 [halothane]$_{blood}$ + 0.71 (r = 0.68; $P < 0.001$; n = 31).

Kates et al., working with isoflurane in a canine preparation designed to isolate left ventricular function, found that the myocardial depressant interactions of isoflurane and verapamil are additive and dose related.[5] Our earlier work administering verapamil as an intravenous bolus
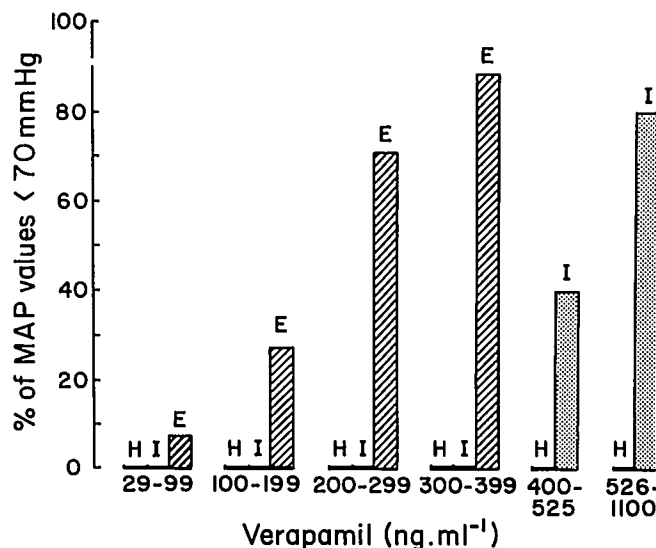

FIG. 2. Percentage of MAP values less than 70 mmHg shown as a function of verapamil level during enflurane (E), isoflurane (I), or halothane (H) anesthesia. Values for n as in Figure 1. E not shown above 400 ng·ml⁻¹ verapamil because of the small number of animals still remaining in the study.

during 0.9% halothane anesthesia showed transient decreases in left ventricular dP/dt and systemic vascular resistance beyond anesthetic control values, with a concomitant decrease in blood pressure, the time course of which appeared to mirror the assumed rise and fall of the plasma verapamil level.[1,2] In this study we have shown that the administration of verapamil by infusion to plasma levels of 500 ng·ml⁻¹ during steady state inhalation anesthesia in the dog resulted in a significant depression of blood pressure, left ventricular dP/dt, and cardiac index during enflurane and isoflurane anesthesia but not during halothane anesthesia, when compared with control anesthetic values. In addition, hemodynamic values obtained with the enflurane–verapamil combination were significantly lower than those observed when similar verapamil levels were achieved during halothane or isoflurane anesthesia. The enflurane group was the only group that had low blood pressures (MAP < 70 mmHg) when verapamil levels were less than 400 ng·ml⁻¹ (fig. 2).

Prolongation of atrioventricular conduction compared with control values reached statistical significance during enflurane and halothane anesthesia. However, over one-half of the enflurane group suffered second degree or higher conduction abnormalities with verapamil plasma levels less than 525 ng·ml⁻¹. While in this model verapamil showed a notable lack of hemodynamic effects during halothane anesthesia, conduction effects were found to be dose related and PR interval prolongation in the halothane group was equivalent to the enflurane group. The effects of verapamil upon hemodynamics (MAP, LV dP/dt, CI) in the enflurane and isoflurane groups have similar slopes (fig. 1). The isoflurane curve is shifted to-

ward higher verapamil levels compared with enflurane when viewed in a dose–response manner (fig. 2).

The observation that values for SVRI during constant infusion in this study were not significantly different from control differs from the highly significant transient decreases in SVR observed immediately after bolus verapamil administration.[1] Neither Kates *et al.*[5] nor Zaggy *et al.*[20] observed sustained decreases in SVR after establishment of a stable verapamil infusion regimen in the presence of isoflurane or halothane, respectively. Possible explanations for this may include preexisting vasodilation by the inhalation anesthetics or homeostatic adaptation to continued exposure to the verapamil–anesthetic combination.

The net effects observed after administering slow channel inhibitors to intact subjects are the result of the direct depressant effects of the drugs modified by homeostatic reflex responses mediated by the autonomic nervous system.[21] Thus, subjects who have autonomic dysfunction, whether on a physiologic basis, an anatomic basis, or a pharmacologic basis, may have interference with these compensatory reflexes and may be at risk for experiencing the direct depressant effects of slow channel inhibitors. In intact subjects, in addition to their direct depressant properties and membrane effects on slow-channel function, the sympatholytic properties of potent inhalation anesthetics also may serve to unmask intrinsic depressant properties of slow-channel inhibitors and contribute to the net anesthetic–drug interaction.

At the anesthetic concentrations achieved in our study, the administration of verapamil by continuous infusion was associated with lower blood pressures and more conduction abnormalities at similar verapamil levels in the enflurane compared with the isoflurane and halothane groups. By design, this study was intended to elucidate the nature of some of the differences in interactions with verapamil among the three halogenated inhalation anesthetics. The lower limit for continued verapamil administration was a MAP of 50 mmHg, thus application of these results to the development of continuous infusion regimens for controlled hypotension, for example, would be limited. The results do emphasize that the slowing of atrioventricular conduction was a prominent effect of verapamil at plasma levels that may or may not be sufficient to result in significant hemodynamic effects.

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