

Cardiovascular Effects of and Interaction Between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs. IV. Chronically Administered Oral Verapamil and Halothane, Enflurane, and Isoflurane

Robert G. Merin, M.D.,* Jacques E. Chelly, M.D.,† Einar S. Hysing, M.D.,‡ Kent Rogers, M.D.,§
Abdallah Dlewti, M.D.,¶ Craig J. Hartley, Ph.D.,** Darrell R. Abernethy, M.D., Ph.D.,**
Marie-Francoise Doursout††

Dogs were chronically instrumented to measure aortic and left atrial blood pressures, left ventricular maximal rate of tension development (dP/dt), cardiac output, and carotid, coronary and renal blood flows. Measurements were taken with the animals awake and during steady-state low and high concentrations of halothane (1.2%, 2.4%), enflurane (2.4%, 4.0%), and isoflurane (1.6%, 3.0%) with and without at least 2 weeks of oral verapamil, 120 mg, three times per day. Plasma verapamil levels varied widely, with means of 500-700 ng · ml⁻¹ in awake animals and lower (300-400 ng · ml⁻¹) at the time of hemodynamic measurements during anesthesia. Chronic oral verapamil in awake dogs produced predominantly tachycardia. The hemodynamic effects of low-dose halothane and isoflurane before and after oral verapamil were unchanged except for decreased renal blood flow after oral verapamil and no coronary vasodilation nor tachycardia. However, left atrial pressure was increased and cardiac output and coronary blood flow were decreased by low concentrations of enflurane with oral verapamil compared to without. The combination of oral verapamil with low (clinical) doses of enflurane was more depressant to the cardiovascular system of healthy dogs than was the combination of verapamil and halothane or isoflurane. (Key words: Anesthetics volatile: enflurane; halothane; isoflurane. Heart: coronary blood flow; ventricular function. Kidney: blood flow. Ions: calcium blocker; verapamil. Pharmacology: drug interactions.)

THE INTERACTION BETWEEN cardioactive drugs and anesthetics is interesting and clinically relevant from two viewpoints. First, drugs such as antiarrhythmics, beta blockers, and calcium channel blockers may be therapeutically useful during anesthesia and surgery. Consequently, documentation of the interaction between such drugs

given intravenously and anesthetics is important. This interaction has been reasonably well documented for the calcium channel blocking drugs, especially verapamil, by several investigations¹⁻⁴ including those from our laboratory.^{5,6} Second, a more frequent clinical problem is the patient who is being treated chronically with calcium channel blockers and who needs surgery and anesthesia. Does the maintenance of calcium channel blocker therapy constitute an increased risk for these patients or, in fact, would the discontinuance of such therapy worsen the condition being treated? The latter can only be answered by clinical studies. However, by observing the effect of the calcium channel blocker verapamil given orally over a prolonged period of time separately and in combination with anesthetics in chronically instrumented dogs, predictions about the behavior of patients in such circumstances may be possible. In addition, by comparing the effect of three different anesthetics in the same animals, a preferential (or detrimental) interaction may be discerned. Consequently, we have used our chronically instrumented dog model to investigate the effect of oral verapamil chronically administered awake and in the presence of halothane, enflurane, and isoflurane.

Materials and Methods

INSTRUMENTATION

Our chronically instrumented dog model has been described in detail,^{5,6} and is approved by the appropriate animal welfare committee. Briefly, healthy, conditioned, mongrel dogs (weighing from 16.5 to 28 kg) were instrumented during halothane anesthesia with: (1) Tygon® catheters in the thoracic aorta and left atrium; (2) pulsed Doppler flow probes on common carotid, circumflex coronary, and renal arteries; (3) an electromagnetic flow probe on the main pulmonary artery; (4) a high-fidelity microtransducer (Konigsberg) in the left ventricle. The dogs were studied more than 2 weeks after surgery when they were afebrile, well trained, and vigorous. Aortic and left atrial and ventricular pressures were transduced through Statham® strain gauges and recorded on a poly-

* Professor.

† Research Assistant Professor.

‡ Visiting Assistant Research Professor.

§ Research Fellow.

¶ Research Fellow.

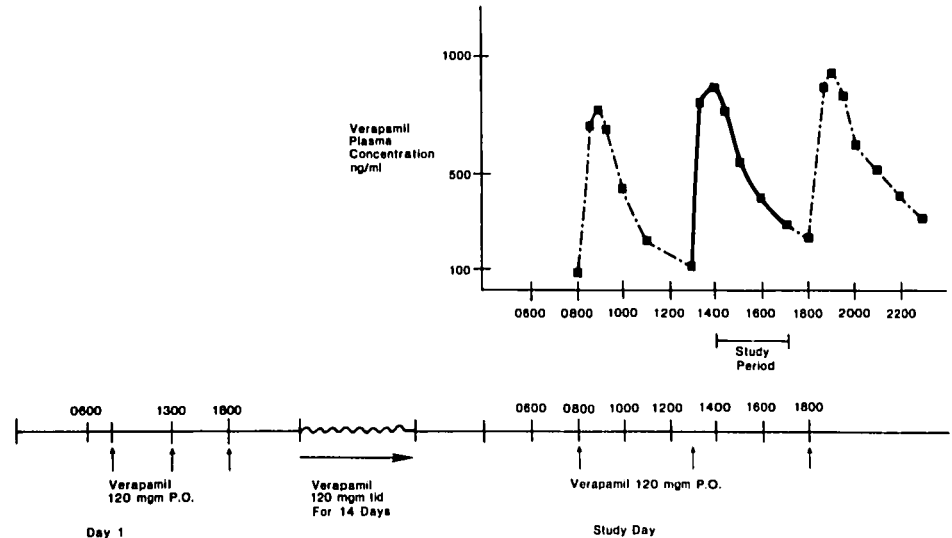
** Associate Professor.

†† Senior Research Assistant.

Received from the Department of Anesthesiology, University of Texas Medical School at Houston,*†‡§ and Departments of Anesthesiology†¶†† and Medicine,** Baylor College of Medicine, Houston, Texas. Accepted for publication August 26, 1986. Presented in part at the 1985 Meeting of the International Anesthesia Research Society, Houston, Texas.

Address reprint requests to Dr. Merin: Department of Anesthesiology, University of Texas Health Science Center at Houston, 6431 Fannin, 5.020 MSMB, Houston, Texas 77030.

FIG. 1. Oral verapamil dosing schedule with typical plasma values on the day of the experiments. *Solid lines* connect actual measured values from one animal. *Dashed lines* connect extrapolated values from typical oral dosing regimens.



graph. The Doppler flows were transduced as the KHz phase shift and recorded on the same polygraph.⁷ The electromagnetic flow probe was transduced through a coupled flowmeter and also recorded on a polygraph. Vascular resistances were calculated as the quotient of arterial blood pressure and measured flows. Plasma verapamil levels were measured using high-pressure liquid chromatography.⁸

EXPERIMENTAL PROTOCOL

Control measurements were made in 12 dogs awake either before the institution of the oral verapamil dosing or at least 1 week after the last dose when neither verapamil nor its major metabolite, norverapamil, could be detected in the dogs' blood. Within that same week, the effects of a low (1.2 MAC: 1.2% halothane; 1.6% isoflurane; 2.4% enflurane end-tidal) and a high (2.4% halothane; 3.0% isoflurane; 4.0% enflurane) anesthetic concentration were recorded as previously described.^{5,6} In the previous studies, the low doses were 1.1–1.2 times MAC to simulate light clinical anesthesia, while the high doses were limited by the maintenance of a mean aortic blood pressure of 50 mmHg. In our dogs, enflurane was the most potent and halothane the least potent in MAC equivalents for aortic hypotension. Verapamil, 120 mg, was administered orally three times a day to each dog after a pilot study showed that relatively consistent peak and trough plasma levels could be produced after 7 days of such dosing. The dosing regimen was continued for at least 2 weeks. One hour after the 1300 h dose (the time of the peak plasma level), the dogs were restudied awake and with the same anesthetic concentrations on different days in random order (fig. 1). Each dog received each anesthetic with and without verapamil. However, all of

the instrumentation was not functioning for every study so that the number of observations was not always 12 (see tables 1–3). At the time of the hemodynamic measurements, blood samples were taken for measurement of plasma verapamil. No attempt was made to regulate the plasma verapamil concentrations, which were decreasing in the typical peak-to-trough fashion seen with oral dosing during the time of the study (fig. 1). Statistical analysis used a repeated-measures analysis of variance and, for paired comparisons, the Bonferroni modification of Student's *t* test. Data are presented as mean \pm SEM.

Results

Plasma verapamil levels after 2 weeks of oral dosing with 120 mg three times a day varied widely between dogs, but the mean was in the high therapeutic range (tables 1–3). Hemodynamic effects were minimal. In general, tachycardia was the only effect seen. There was no difference in these hemodynamic effects whether the verapamil effect was measured before or after the anesthetic dosing.

The effects of the inhaled anesthetics without verapamil were the same as noted in previous studies^{5,6,9–11} and remarkably similar (tables 1–3). During low concentrations, the tachycardia produced generally overcame the negative inotropic effect of these drugs, but, at the high concentrations, a definite negative inotropic effect was seen as indicated by decreased cardiac output, left ventricular maximal rate of tension development (dP/dt), mean aortic pressure, and increased left atrial pressure. Regional blood flows were generally well preserved except for the decreases in carotid blood flow at high anesthetic concentrations.

TABLE 1. Interaction of Oral Verapamil and Halothane

	Conscious		Halothane			
		+ Verapamil	Low		High	
				+ Verapamil	Verapamil	+ Verapamil
HR (min ⁻¹)	84 ± 6	106 ± 12*	93 ± 5	84 ± 5	112 ± 4**†	85 ± 5‡
MAP (mmHg)	97 ± 4	90 ± 4	73 ± 3*	66 ± 4§	51 ± 3**†	35 ± 2‡,§,¶
LAP (mmHg)	3.8 ± 0.9 (11)	6.4 ± 2 (9)	5.1 ± 0.7 (11)	8.4 ± 2 (10)	8.8 ± 1.2 (10)**†	8 ± 0.7 (10)
CO (l·min ⁻¹)	1.57 ± 0.1 (7)	1.79 ± 0.1 (5)	1.41 ± 0.1 (7)	1.33 ± 0.1 (5)	1.01 ± 0.2**† (7)	0.73 ± 0.0§¶ (5)
SV (ml)	21 ± 1 (7)	21 ± 4 (5)	15.7 ± 1 (7)	16.3 ± 1 (5)	15.5 ± 6 (7)	9.2 ± 4¶ (5)
dP/dt (mmHg·min ⁻¹)	3100 ± 150 (11)	2620 ± 250 (11)	1670 ± 180* (11)	1420 ± 120 § (10)	840 ± 80**† (11)	650 ± 50§¶ (10)
SVR (mmHg/l/min)	63 ± 6 (7)	50.7 ± 3 (5)	50.9 ± 5 (7)	47 ± 4 (5)	50.8 ± 8 (7)	47.8 ± 1.6 (5)
CaF (ml·min ⁻¹)	134 ± 11 (10)	169 ± 12* (9)	153 ± 13 (10)	166 ± 14 (9)	143 ± 9 (10)	114 ± 12 (9)
CaVR (mmHg/ml/min)	0.77 ± 0.1	0.55 ± 0.1*	0.5 ± 0.04*	0.43 ± 0	0.38 ± 0*	0.34 ± 0§
CoF (ml·min ⁻¹)	35 ± 6 (8)	42 ± 11 (8)	31 ± 6 (8)	27 ± 6 (8)	30 ± 5 (8)	21 ± 3 (8)
CoVR (mmHg/ml/min)	3.3 ± 0.4	3.0 ± 0.7	2.6 ± 0.3*	3.05 ± 0.4	1.9 ± 0.2**†	1.95 ± 0.2§
ReF (ml·min ⁻¹)	108 ± 14	89 ± 12 (11)	107 ± 15	78 ± 9† (11)	88 ± 12	48 ± 7‡,§¶ (11)
ReVR (mmHg/ml/min)	1 ± 0.2	1.2 ± 0.2	0.9 ± 0.2	0.94 ± 0.1	0.67 ± 0.1*	0.87 ± 0.1§
V pl (ng·ml ⁻¹)	—	538 ± 126	—	442 ± 142	—	469 ± 153
NV pl (ng·ml ⁻¹)	—	1019 ± 173	—	850 ± 174	—	868 ± 174

HR = heart rate; MAP = mean aortic blood pressure; LAP = left atrial blood pressure; CO = cardiac output; SV = stroke volume; dP/dt = maximal rate of rise of left ventricular blood pressure; SVR = systemic vascular resistance; CaF = carotid artery blood flow; CaVR = carotid artery vascular resistance; CoF = coronary artery blood flow; CoVR = coronary artery vascular resistance; ReF = renal artery blood flow; ReVR = renal artery vascular resistance; V pl = plasma verapamil concentration; NV pl = norverapamil plasma concentration.

Numbers in parentheses are number of measurements, if different from 12, ± = SEM.

* $P < 0.05$ vs. awake.

† $P < 0.05$ vs. low anesthetic concentration.

‡ $P < 0.05$ vs. high anesthetic concentration.

§ $P < 0.05$ vs. verapamil awake.

¶ $P < 0.05$ vs. verapamil at low anesthetic concentration.

In spite of the fact that plasma verapamil levels were generally lower during anesthesia than awake (see fig. 1), there were definite effects seen with oral dosing (tables 1-3). When compared with verapamil awake, after oral verapamil dosing all three anesthetics depressed mean arterial pressure and left ventricular dP/dt at both concentrations and cardiac output at the high concentrations (tables 1-3). Low concentrations of halothane produced no other significant effects after oral verapamil dosing that were not seen without verapamil, while low-dose isoflurane only depressed renal blood flow and vascular resistance more with verapamil than without. However, low concentrations of enflurane decreased cardiac output and coronary and renal blood flow and increased left atrial

pressure after verapamil dosing, whereas these effects had not been seen at the same anesthetic concentrations with the oral verapamil. Table 4 dramatically demonstrates the different effect of low concentrations of enflurane versus awake compared with isoflurane and halothane after oral verapamil dosing.

When the same anesthetic concentrations were compared with and without oral verapamil, all three anesthetics decreased heart rate and renal blood flow at high concentrations more after oral verapamil, and halothane also decreased mean arterial pressure to a greater extent (table 5). At low concentrations, the effect of oral verapamil was more pronounced during enflurane anesthesia because heart rate, mean aortic pressure, left ventricular

TABLE 2. Interaction of Oral Verapamil and Enflurane

	Conscious		Enflurane			
		+ Verapamil	Low		High	
				+ Verapamil		+ Verapamil
HR (min ⁻¹)	77 ± 4	88 ± 8	102 ± 5*	81 ± 7†	111 ± 6* (10)	91 ± 7‡ (10)
MAP (mmHg)	92 ± 4	90 ± 5	72 ± 3*	58 ± 4†·§	50 ± 2*† (10)	41 ± 2§·¶ (10)
LAP (mmHg)	5.1 ± 1 (10)	4.6 ± 1.2 (10)	4.8 ± 1.1 (9)	7 ± 1.4 § (10)	8.3 ± 1.6† (9)	8 ± 1 § (9)
CO (l·min ⁻¹)	1.77 ± 0.1 (7)	1.83 ± 0.2 (5)	1.6 ± 0.1 (7)	1.33 ± 0.2 § (5)	1.11 ± 0.1* (5)	0.93 ± 0.1 § (5)
SV (ml)	25 ± 1.5 (7)	23.4 ± 1.7 (5)	16.7 ± 1 (7)	16.6 ± 1 (5)	11.1 ± 3.4*† (5)	12.9 ± 3.5 (5)
dP/dt (mmHg·sec ⁻¹)	3170 ± 190 (10)	2650 ± 330 (10)	1560 ± 80* (10)	1190 ± 120†·§ (10)	890 ± 100*† (8)	800 ± 110 §·¶ (9)
SVR (mmHg/l/min)	54.1 ± 4.5 (7)	50.5 ± 6 (6)	41.9 ± 2 (7)	37.9 ± 5 (5)	43.9 ± 1.9 (5)	41 ± 5.4 (5)
CaF (ml·min ⁻¹)	151 ± 12 (10)	176 ± 11 (8)	172 ± 13 (10)	162 ± 13 (9)	127 ± 14† (9)	132 ± 14 (8)
CaVR (mmHg/ml/min)	0.65 ± 0.1	0.54 ± 0.1	0.68 ± 0.2	0.38 ± .04 §	0.45 ± .03*	0.36 ± .05 §
CoF (ml·min ⁻¹)	36 ± 5 (9)	39 ± 5 (8)	37 ± 7 (9)	23 ± 4 § (8)	27 ± 5 (8)	19 ± 4 § (7)
CoVR (mmHg/ml/min)	2.9 ± 0.4	2.4 ± 0.4	2.6 ± 0.5	3.0 ± 0.5	2.3 ± 0.5	2.6 ± 0.4
ReF (ml·min ⁻¹)	89 ± 12	89 ± 11 (11)	84 ± 10	64 ± 8 §† (11)	73 ± 11 (10)	47 ± 5 ‡·§ (9)
ReVR (mmHg/ml/min)	1.2 ± 0.1	1.3 ± 0.2	0.98 ± 0.1	0.99 ± 0.12	0.9 ± 0.2	1.1 ± 0.2
V-pl (ng·ml ⁻¹)	—	655 ± 246	—	434 ± 173	—	277 ± 136 (10)
N-V pl (ng·ml ⁻¹)	—	954 ± 252	—	799 ± 213	—	651 ± 206 (10)

See table 1 for abbreviations.

* $P < 0.05$ vs. awake.

† $P < 0.05$ vs. low anesthetic concentration.

‡ $P < 0.05$ vs. high anesthetic concentration.

§ $P < 0.05$ vs. verapamil awake.

¶ $P < 0.05$ vs. verapamil at low anesthetic concentration.

dP/dt, and renal blood were significantly lower. During low-dose halothane and isoflurane, only renal blood was decreased after oral verapamil.

Discussion

Verapamil has been shown to be effective treatment given orally and chronically for angina pectoris,¹² paroxysmal supraventricular tachycardia,¹³ hypertrophic obstructive cardiomyopathy,¹⁴ and atrial fibrillation.¹⁵ Consequently, many patients are scheduled for anesthesia and surgery while being chronically treated with the drug. The most important question to be answered by these experiments is: Does chronic oral verapamil therapy significantly alter the cardiovascular effect of inhalation anesthetics? A statistical comparison of the effect of both low and high concentrations of the three clinically used inhalation anesthetics without and with chronic verapamil treatment suggests that the effect of such treatment is

minimal (table 5). Low concentrations of enflurane decreased heart rate, mean aortic pressure, and left ventricular dP/dt and renal blood flow more with verapamil than without, while equivalent concentrations of halothane and isoflurane only decreased renal blood flow with oral verapamil compared to without. There were even fewer differences during high concentrations of the anesthetics. All three anesthetics produced a greater decrease in heart rate and renal blood flow, while halothane had a more depressant effect on mean aortic pressure after oral verapamil.

Another view of the question can be obtained by examining the effect of the anesthetics before and after oral verapamil compared with their respective awake states (table 4). The major differences produced by the anesthetics after oral verapamil but not before were: halothane decreased carotid and renal blood flow at high concentrations; enflurane increased left atrial pressure and decreased cardiac output, coronary vascular resistance, and

TABLE 3. Interaction of Oral Verapamil and Isoflurane

	Conscious		Isoflurane			
		+ Verapamil	Low		High	
				+ Verapamil		+ Verapamil
HR (min ⁻¹)	81 ± 5	97 ± 9*	103 ± 4*	85 ± 6	104 ± 2*	84 ± 7‡
MAP (mmHg)	96 ± 3	94 ± 5 (11)	73 ± 2*	70 ± 4 §	49 ± 3*†	42 ± 3 §¶
LAP (mmHg)	2.8 ± 0.9 (11)	3.4 ± 0.8 (9)	2.6 ± 0.4	5.3 ± 1 (9)	4.9 ± 0.9†	5.7 ± 0.8 (9)
CO (L · min ⁻¹)	1.64 ± 0.2 (7)	1.80 ± 0.2 (5)	1.63 ± 0.1 (7)	1.35 ± 0.1 (5)	1.39 ± 0.1*† (7)	1.09 ± 0.1 § (5)
SV (ml)	22.7 ± 2 (7)	19.5 ± 1 (5)	16.5 ± (7)*	18.6 ± 1.5 (5)	13.8 ± 0.1.2*† (7)	15.7 ± 1.3 (5)
dP/dt (mmHg · sec ⁻¹)	3090 ± 150 (11)	2700 ± 240 (10)	1910 ± 150* (11)	1590 ± 150 § (11)	1130 ± 90*† (11)	960 ± 120 §¶ (11)
SVR	62.8 ± 7 (7)	56.4 ± 8 (5)	44 ± 3.3* (7)	47.7 ± 2.6 (5)	34.5 ± 2.9*† (7)	43.3 ± 6.2 (5)
CaF (ml · min ⁻¹)	156 ± 11 (10)	165 ± 16 (9)	168 ± 16 (10)	178 ± 12 (9)	127 ± 15* (10)	132 ± 13 § (9)
CaVR (mmHg/ml/min)	0.61 ± 0.1	0.62 ± 0.1	0.47 ± 0	0.35 ± 0.1	0.45 ± 0	0.34 ± 0
CoF (ml · min ⁻¹)	35 ± 5 (9)	45 ± 8 (8)	44 ± 9 (9)	38 ± 8 (8)	41 ± 6 (9)	34 ± 9¶ (7)
CoVR (mmHg/ml/min)	3.3 ± 0.5	2.6 ± 0.4	2.0 ± 0.3*	2.2 ± 0.4	1.34 ± 0.1*†	1.7 ± 0.4¶
Ref (ml · min ⁻¹)	102 ± 14	74 ± 9 (11)	98 ± 12	65 ± 7† § (11)	79 ± 12	48 ± 5‡ §¶ (11)
ReVR (mmHg/ml/min)	1.1 ± 0.2	1.55 ± 0.2	0.9 ± 0.1	1.02 ± 0.1 §	0.79 ± 0.1	0.9 ± 0.1 §
V pl (ng · ml ⁻¹)	—	731 ± 264	—	445 ± 154	—	387 ± 129
N-V pl (ng · ml ⁻¹)	—	1114 ± 268	—	942 ± 251	—	871 ± 183

See table 1 for abbreviations.

* P < 0.05 vs. awake.

† P < 0.05 vs. low anesthetic concentration.

‡ P < 0.05 vs. high anesthetic concentration.

§ P < 0.05 vs. verapamil awake.

¶ P < 0.05 vs. verapamil at low anesthetic concentration.

coronary and renal blood flow at low concentrations and increased left atrial pressure and decreased coronary and renal blood flow at high concentrations; isoflurane decreased renal blood flow and vascular resistance at low

concentrations and carotid blood flow, renal blood flow, and renal vascular resistance at high concentrations. In addition, chronic oral verapamil therapy ablated the tachycardia produced by all three anesthetics at both concentrations. This tachycardia has previously been shown to overcome partially the direct negative inotropic effect of halothane⁹ (and presumably enflurane¹⁰ and isoflurane¹¹) at low anesthetic concentrations. Apparently, in our dogs, only with enflurane was this tachycardia responsible for maintaining cardiac function because the earlier mentioned ablation did not alter the effect of low concentrations of halothane and isoflurane.

There were also some differences in effects on regional blood flow and resistance with all anesthetics. Treatment with oral verapamil abolished the coronary vasodilating effects of halothane and isoflurane, whereas all three anesthetics depressed renal blood flow after oral verapamil, but not before. In previous experiments in our laboratory, renal blood flow was preserved in chronically instrumented dogs until a mean aortic pressure of less than 50 mmHg was reached with all three anesthetics.^{5,6,16} Because

TABLE 4. Significant Effects of Low Anesthetic Concentration Compared with Conscious Controls with (but not without) Oral Verapamil

	Halothane	Enflurane	Isoflurane
HR	—	—	—
MAP	—	—	—
LAP (mmHg)	—	2.4 ± 1	—
CO (ml · min ⁻¹)	—	-500 ± 100	—
SV	—	—	—
dP/dt	—	—	—
SVR	—	—	—
CaF	—	—	—
CaVR	—	—	—
CoF (ml · min ⁻¹)	—	-16 ± 4	—
CoVR	—	—	—
ReF (ml · min ⁻¹)	—	-25 ± 6	-26 ± 7
ReVR (mmHg/ml/min)	—	—	-0.6 ± 0.2

See table 1 for abbreviations.

TABLE 5. Significant Effects of Oral Verapamil at the Same Anesthetic Concentrations

	Low			High		
	Halothane	Enflurane	Isoflurane	Halothane	Enflurane	Isoflurane
HR (min ⁻¹)	—	-21 ± 6	—	-27 ± 5	-21 ± 5	-20 ± 6
MAP (mmHg)	—	-14 ± 4	—	-16 ± 3	—	—
LAP	—	—	—	—	—	—
CO	—	—	—	—	—	—
SV	—	—	—	—	—	—
dP/dt (mmHg · min ⁻¹)	—	-400 ± 140	—	—	—	—
SVR	—	—	—	—	—	—
CaF	—	—	—	—	—	—
CaVR	—	—	—	—	—	—
CoF	—	—	—	—	—	—
CoVF	—	—	—	—	—	—
ReF (ml · min ⁻¹)	-34 ± 10	-23 ± 10	-37 ± 12	-43 ± 7	-31 ± 8	-35 ± 10
ReVR	—	—	—	—	—	—

See table 1 for abbreviations.

verapamil has been shown to abolish renal autoregulation in pentobarbital-anesthetized dogs,¹⁷ we suggest that the same effect was seen with the three inhalation anesthetics as well.

In our previous investigations, we suggested that the combination of high anesthetic concentrations and both low- and high-dose intravenous verapamil infusion was particularly depressant to our dogs' cardiovascular systems.^{5,6} Although oral verapamil did result in lower heart rates and renal blood flow during high anesthetic concentrations, the effects were less pronounced than those seen with intravenous verapamil. In addition, plasma verapamil levels were generally higher after the oral dosing than even the high-dose intravenous verapamil (table 6). Even so, at no time, even with plasma verapamil levels in excess of 1,000 ng · ml⁻¹ (in two animals >2000 ng · ml⁻¹), were any episodes of severe bradycardia (<50 min⁻¹) and atrioventricular (AV) block observed as had been seen frequently, especially with enflurane, in our intravenous studies.⁶ This observation is unexpected, because in the intravenous study arrhythmias appeared predominantly

in dogs with high plasma verapamil levels. However, as with the intravenous dosing, the combination of oral verapamil with low-dose enflurane appeared to be more depressant to cardiac function than with low-dose halothane or isoflurane. Bonow *et al.* also reported that the cardiodynamic effects of chronically administered oral verapamil were different from those produced by the same blood levels of intravenously administered drug in patients with hypertrophic cardiomyopathy.¹⁴ During intravenous dosing, the predominant effect of verapamil was a decrease in systolic function of the heart, while after chronic oral dosing, the major effect was on diastolic function.

Whereas steady-state plasma levels can be established with intravenous infusion of verapamil,¹⁻⁶ chronic oral dosing results in a pattern of recurrent peaks and troughs (fig. 1). The measured plasma levels of verapamil were generally lower during the anesthetics than during the awake controls because the measurements during anesthesia were made after the measurement of the awake-state hemodynamics. In several animals, the awake-state observations were made later at a time corresponding to the second anesthetic measurement and the hemodynamics were similar. Another difference between the intravenous infusion and oral dosing is the presence of the major metabolite of verapamil, norverapamil. In fact, norverapamil levels were generally higher than verapamil (tables 1-3). Norverapamil is generally considered to possess about 20% of the calcium blocking potency of the parent compound, so it is certainly possible that norverapamil was also exerting an effect in these studies. However, such an effect should also be expected in patients taking oral verapamil chronically.¹⁸

In summary, if the results of these experiments in healthy dogs can be extrapolated to patients being treated with chronically administered verapamil, then: 1) Clinical (low) doses of enflurane should be expected to produce

TABLE 6. Plasma Verapamil Concentration (ng · ml⁻¹)

	Intravenous Infusion		Chronic Oral 120 mg tid
	3 μg · kg ⁻¹ · min ⁻¹	6 μg · kg ⁻¹ · min ⁻¹	
Halothane			
Low	132 ± 2	229 ± 23	442 ± 142
High	155 ± 15	324 ± 34	469 ± 153
Enflurane			
Low	139 ± 13	326 ± 34	434 ± 173
High	164 ± 17	339 ± 38	277 ± 136
Isoflurane			
Low	117 ± 11	220 ± 21	445 ± 154
High	130 ± 18	269 ± 31	387 ± 129

more cardiac depression than isoflurane or halothane in such patients; 2) a decrease in renal blood flow should be expected with all three anesthetics; and 3) the cardiovascular effect of the combination of chronic oral verapamil and the inhalation anesthetics appears to be less than previously observed with the intravenous administration of the drug.²⁻⁶ In particular, no episodes of severe bradycardia and AV dissociation were observed after oral verapamil dosing. 4) Finally, the minimal effects during low (clinical) dose anesthesia after oral verapamil support the practice of continuing calcium channel blocking drug therapy on the day of surgery.

References

1. Kapur PA, Flacke WE: Epinephrine-induced arrhythmias and cardiovascular function after verapamil during halothane anesthesia in the dog. *ANESTHESIOLOGY* 55:219-225, 1981
2. Kates RA, Zaggy AP, Norfleet EA, Heath KR: Comparative cardiovascular effects of verapamil, nifedipine and diltiazem during halothane anesthesia in swine. *ANESTHESIOLOGY* 61:10-18, 1984
3. Kapur PA, Bloor BC, Flacke WE, Olewine SK: Comparison of cardiovascular responses to verapamil during enflurane, isoflurane, or halothane anesthesia in the dog. *ANESTHESIOLOGY* 61:156-160, 1984
4. Kates RA, Kaplan JA, Guyton RA, Dorsey L, Hug CC, Hatcher CR: Hemodynamic interactions of verapamil and isoflurane. *ANESTHESIOLOGY* 59:132-138, 1983
5. Chelly JE, Rogers K, Hysing ES, Taylor A, Hartley C, Merin RG: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. I. Verapamil and halothane. *ANESTHESIOLOGY* 64:560-567, 1986
6. Rogers K, Hysing ES, Merin RG, Taylor A, Hartley C, Chelly JE: Cardiovascular effects of and interaction between calcium blocking drugs and anesthetics in chronically instrumented dogs. II. Verapamil, enflurane and isoflurane. *ANESTHESIOLOGY* 64:568-575, 1986
7. Hartley CJ, Lewis RM, Ishida T, Chelly JE, Entman ML: High frequency pulsed Doppler measurements of blood flow and myocardial dimensions in conscious animals, Cardiovascular Instrumentation, Applicability of New Technology to Behavioral Research. Edited by Herd JA, Grotto AM, Kauffman PG, Weiss SM. Bethesda, NIH Publications #84-165, US Dept HHS, 1984, pp 95-106
8. Harapat SR, Kates RE: High performance liquid chromatographic analysis of verapamil. II. Simultaneous quantitation of verapamil and its active metabolite, norverapamil. *J Chromatogr* 181:484-489, 1980
9. Merin RG, Kumazawa T, Luka NL: Myocardial function and metabolism in the conscious dog and during halothane anesthesia. *ANESTHESIOLOGY* 44:401-413, 1976
10. Merin RG, Kumazawa T, Luka NL: Enflurane depresses myocardial function, perfusion and metabolism in the dog. *ANESTHESIOLOGY* 45:501-507, 1976
11. Merin RG: Are the myocardial functional and metabolic effects of isoflurane really different from those of halothane and enflurane? *ANESTHESIOLOGY* 55:398-408, 1981
12. Subramanian B, Bowles M, Lahiri A, Davies AB, Raftery EB: Long-term antianginal action of verapamil assessed with quantitated serial treadmill stress testing. *Am J Cardiol* 48:529-535, 1981
13. Sakurai M, Yasuda H, Kato N, Nomura A, Fujita M, Nishino T, Fujita K, Koike Y, Saito H: Chronic and acute effects of verapamil in patients with paroxysmal supraventricular tachycardia. *Am Heart J* 105:619-628, 1983
14. Bonow RO, Rosing DR, Epstein SE: The acute and chronic effects of verapamil on left ventricular function in patients with hypertrophic cardiomyopathy. *Eur Heart J* 4(Suppl F):57-65, 1983
15. Lang R, Klein HO, Weiss E, David D, Sareli P, Levy A, Guerrero J, DiSegni E, Kaplinsky E: Superiority of oral verapamil therapy to digoxin in treatment of chronic atrial fibrillation. *Chest* 83:491-499, 1983
16. Hysing ES, Chelly JE, Jacobson L, Hartley C, Merin RG: Renal blood flow during enflurane, halothane and isoflurane in chronically instrumented dogs (abstract). *Acta Anaesthesiol Scand* 29(Suppl 80):73, 1985
17. Navar LG, Champion WJ, Thomas CE: Effects of calcium channel blockade on renal vascular resistance responses to changes in perfusion pressures and angiotensin-converting enzyme inhibition in dogs. *Circ Res* 58:874-881, 1986
18. Hamann SR, Blouin RA, McAllister RG: Clinical pharmacokinetics of verapamil. *Clin Pharmacokinet* 9:26-41, 1984