

Cardiovascular Effects of and Interaction Between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs: VII. Verapamil and Thiopental

Douglas C. Hill, M.D.,* Patrick F. Wouters, M.D.,† Jacques E. Chelly, M.D., Ph.D.,‡
Marie-Francoise Doursout, Ph.D.,§ Darrell R. Abernethy, M.D., Ph.D.,¶
Craig J. Hartley, Ph.D.,** Robert G. Merin, M.D.††

To assess the role of basal anesthesia in the negative inotropic properties of verapamil, the effect of thiopental (30 mg/kg followed by $3.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) on verapamil pharmacokinetics ($200 \text{ } \mu\text{g}/\text{kg}$ iv; $n = 6$) and its pharmacodynamics (3 and $6 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; $n = 11$) in chronically instrumented dogs was studied. In the presence of thiopental, verapamil pharmacokinetics remained essentially unchanged. In contrast, anesthesia altered verapamil hemodynamic properties. In the conscious animal verapamil infusions increased heart rate (14 ± 3 and 27 ± 4 beats/min, respectively), cardiac output (0.22 ± 0.07 and 0.24 ± 0.08 , l/min, respectively) and PR interval (14 ± 2 and 25 ± 6 ms, respectively) and slightly decreased dP/dt (-315 ± 114 and -419 ± 106 mmHg/s, respectively). Systemic vascular resistance (SVR) decreased at the low dose (-2.7 ± 0.7 mmHg \cdot l \cdot min $^{-1}$), and stroke volume decreased at the high dose (-4.4 ± 0.6 ml). Yet the presence of thiopental resulted in an accentuation of verapamil-induced tachycardia (27 ± 7 and 31 ± 6 beats/min, respectively), and a decrease in stroke volume (-5.3 ± 2.0 and -6.3 ± 2.1 ml, respectively). At $3 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ verapamil did not increase PR interval, cardiac output, or vasodilation. Finally, at $6 \text{ } \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ verapamil did not decrease dP/dt and increased renal blood flow (21.8 ± 6.4 ml/min). These data provide evidence that the negative inotropic properties of verapamil are more pronounced in the presence of thiopental. However, the role of basal anesthesia appears to be limited. (Key words: Anesthetics, intravenous: thio-

pental. Heart: ventricular function. Interactions: drug. Pharmacokinetics: verapamil. Pharmacology: calcium channel blocking drug; verapamil.)

DEPENDING on the experimental conditions, conflicting data on the magnitude of the cardiac depression induced by verapamil have been reported. In chronically instrumented dogs verapamil, in clinically significant plasma concentrations, is well tolerated in the presence of low-dose inhalation anesthetics.¹⁻³ In contrast, several investigators have demonstrated that verapamil induced a profound cardiac depression in acutely instrumented dogs anesthetized with even lower doses of halothane, isoflurane, or enflurane.⁴⁻⁶ Possible explanations for the discrepancies between our data¹⁻³ and those collected in acutely instrumented animals include the consequences of acute instrumentation, surgical stress, and the use of basal anesthesia.⁷ Thiopental, the most frequently used basal anesthetic, depresses myocardial contractility *in vitro* and *in vivo*.^{8,9} In addition, thiopental directly affects the baroreceptor reflexes and the autonomic nervous system function.^{10,11} Because the hemodynamic response to verapamil represents the balance between its direct cardiac properties and the reflexly mediated stimulation of the sympathetic tone, it is possible that the use of thiopental for basal anesthesia affects verapamil properties.¹²

We hypothesized that thiopental accentuated the negative inotropic properties of verapamil. Because inhalational anesthetics affect both the pharmacokinetic and pharmacodynamic properties of calcium channel blockers,¹⁻⁶ we decided to assess the effects of thiopental on verapamil pharmacokinetics and pharmacodynamics in chronically instrumented dogs.

Methods

INSTRUMENTATION

The study was approved by the Baylor College of Medicine Animal Care Program. A description of the basic model has been published.^{1,3} Briefly, 11 healthy mongrel dogs, free of heart worms and weighing 15.8-27 kg, were

* Research Fellow, Department of Anesthesiology, University of Texas Medical School at Houston. Present address: Department of Anesthesiology, St. Mark's Hospital, Salt Lake City, Utah.

† Research Fellow, Department of Anesthesiology, University of Texas Medical School at Houston. Present address: Department of Anesthesia, Katholieke Universiteit Leuven Gasthuisberg, Belgium.

‡ Professor, Departments of Anesthesiology and Pharmacology, and Division of Clinical Pharmacology, University of Texas Medical School at Houston.

§ Research Assistant Professor, Department of Anesthesiology, Baylor College of Medicine.

¶ Associate Professor, Department of Medicine, Baylor College of Medicine. Present address: Department of Medicine, Brown University Medical School, Providence, Rhode Island.

** Professor, Department of Medicine, Baylor College of Medicine.

†† Professor, Department of Anesthesiology, University of Texas Medical School at Houston.

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Address reprint requests to Dr. Chelly: Department of Anesthesiology, University of Texas Medical School, 6431 Fannin, 5.020 MSMB, Houston, Texas 77030.

instrumented as follows: Tygon catheters (Tygon, Norton Inc., Akron, Ohio) in the left atrium and thoracic aorta, an electromagnetic flow probe (Micron Inc., Los Angeles, California) around the pulmonary artery, a high-fidelity pressure transducer (Konigsberg Inc., Pasadena, California) in the left ventricular cavity, and pulsed Doppler flow probes (Baylor College of Medicine, Houston, Texas) around the coronary, renal, and common carotid arteries. All animals were studied at least 10 days after surgery, when they were afebrile and trained to lie quietly.

Aortic, left ventricular and left atrial pressures, cardiac output, and coronary, renal, and carotid blood flows were continuously recorded on a Gould polygraph (Gould Inc., Cleveland, Ohio). Cardiac output was measured with a Micron RC 1000 electromagnetic flowmeter. The kilohertz output of the pulsed Doppler flowmeters has been shown to be linearly related to volume flow for a variety of flow probe sizes. Left ventricular dP/dt was derived electronically.

PROTOCOLS

Doses for maintaining steady-state thiopental anesthesia were calculated according to previously published data on the pharmacokinetic and anesthetic properties of thiopental in mongrel dogs.^{13,14} In all protocols thiopental was administered at 30 mg/kg followed by 3.5 mg \cdot kg⁻¹ \cdot h⁻¹ iv.

Experiment A: Effects of thiopental on verapamil pharmacokinetics. Six dogs received verapamil over 10 min, 200 μ g/kg awake and at least 20 min after induction of thiopental anesthesia on two occasions separated by at least 4 days and in random order.

Aortic blood samples were collected prior to and 1, 3, 5, 10, 15, 30, and 45 min and 1, 2, 3, 4, and 5 h after verapamil.

Experiment B. Effects of thiopental on hemodynamic responses to verapamil infusions. Eleven dogs received two steady-state infusions of verapamil (200 μ g/kg iv over 3 min followed by 3 μ g \cdot kg⁻¹ \cdot min⁻¹ for 27 min, then another 200 μ g/kg over 3 min followed by 6 μ g \cdot kg⁻¹ \cdot min⁻¹ for 27 min) awake and during thiopental anesthesia on two occasions. Hemodynamic values and aortic blood samples were collected before and after 30 min of the 3 μ g \cdot kg⁻¹ \cdot min⁻¹ and 6 μ g \cdot kg⁻¹ \cdot min⁻¹ verapamil infusions.

Experiment C. Hemodynamic effects of thiopental infusion. Five dogs were anesthetized with thiopental. Hemodynamic values were collected 20 min after induction of anesthesia and after 30 and 60 additional min (to mimic the total duration of the verapamil infusions in experiment B).

After induction of anesthesia, the trachea of each animal was intubated and the lungs were ventilated with a

mixture of oxygen and nitrogen, using a Harvard ventilator (Harvard Apparatus, South Natick, Massachusetts) at the tidal volume of 10–15 ml/kg with the rate adjusted to maintain arterial blood gases and pH as in the awake state. During anesthesia the animals were placed in a right lateral decubitus position (the same position as awake) and received 3–5 ml \cdot kg⁻¹ \cdot h⁻¹ lactated Ringer's solution during the experiment. End-tidal carbon dioxide concentration was continuously monitored using infrared absorption techniques (Lifespan 100, Biochem International, Inc., Waukesha, Wisconsin). Arterial blood gas determinations were intermittently made with a Radiometer ABC[®] electrode system (Radiometer Inc., Denmark). Finally, rectal temperature was measured with a thermocouple probe (Yellow Springs Instruments, Yellow Springs, Ohio).

SAMPLE ANALYSIS

Blood specimens for verapamil were drawn into "venoject" (Becton-Dickinson, Rutherford, New York) heparinized tubes, centrifuged, and the plasma separated and stored at -20° C until analyzed. Concentrations of verapamil were analyzed by gas-liquid chromatography using nitrogen-phosphorus detection. Interassay variability was less than 10% at all concentrations.¹⁵

PHARMACOKINETIC DATA ANALYSIS

After iv verapamil infusion, postinfusion plasma drug concentrations (C) were fitted to equations formed by a linear sum of two exponential terms using iterative weighted ($1/C^2$) nonlinear least-squares regression analysis. The program used was MLAB in the PROPHET network. After correction of the derived coefficients for the infusion time,¹⁶ the pharmacokinetic functions were used to calculate the elimination half-life, total apparent volume of distribution using the steady state method, and total clearance.¹⁷ In addition, central compartment volume (V_1) and the microrate constant, describing movement of verapamil from central to peripheral compartments (K_{12}), were determined from the pharmacokinetic function, and intercompartmental clearance (Q) from the central compartment was determined by the relationship: $Q = K_{12} \times V_1$.¹⁸

STATISTICAL ANALYSIS

The effects of verapamil and thiopental alone and in combination were analyzed using a two-way analysis of variance. Alpha was set at a level of 0.05. When significant, multiple paired comparisons were applied. However, for each paired comparison, the appropriate level of alpha was determined according to the Bonferroni method.¹⁹ Data are presented as mean \pm SEM.

TABLE 1. Effects of Thiopental on Verapamil Pharmacokinetics

	Verapamil	Verapamil + Thiopental
Initial volume of distribution (l)	40 ± 4	49 ± 6
Intercompartmental clearance (l/h)	211 ± 36	372 ± 55
Volume of distribution at steady state (l)	101 ± 17	134 ± 22
Total clearance (l/h)	54 ± 6	73 ± 9
Elimination half-life (h)	1.64 ± 0.27	1.52 ± 0.23

Values are mean ± SEM; n = 6.

Results

EXPERIMENT A

Steady-state thiopental infusions did not affect initial volume of distribution, intercompartmental clearance, volume of distribution at steady state, total clearance, and elimination half-life of verapamil (table 1).

EXPERIMENT B

In awake dogs, 3 and 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ of verapamil induced a dose-dependent and significant increase in heart rate (from 84 ± 3 to 98 ± 4 and 112 ± 5 beats/min, respectively), and PR interval (from 111 ± 4 to 126 ± 4 and 136 ± 7 ms, respectively), an increase in cardiac output (from 2.1 ± 0.3 to 2.4 ± 0.3 and 2.2 ± 0.2 l/min, respectively) and a dose-dependent and slight decrease in dP/dt (from $3,360 \pm 119$ to $3,046 \pm 161$ and $2,941 \pm 29$ mmHg/s, respectively) (figs. 1 and 2). In addition, we recorded a decrease in systemic vascular resistance (from 50 ± 6 to 45 ± 6 mmHg $\cdot \text{min}^{-1} \cdot \text{l}^{-1}$) and stroke volume (from 26 ± 3 to 22 ± 4 ml) at the low and high dose, respectively.

Steady-state thiopental anesthesia significantly decreased only dP/dt (from $3,265 \pm 134$ to $2,447 \pm 173$ mmHg/s). In the presence of thiopental, verapamil produced a more profound increase in heart rate at both the low and high dose (from 98 ± 5 to 125 ± 6 and 144 ± 5 beats/min, respectively). In addition, verapamil at 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ produced a significant increase in PR interval (from 114 ± 5 to 126 ± 6 ms) and decrease in dP/dt (from $2,447 \pm 173$ to $2,156 \pm 134$ mmHg/s) and stroke volume (from 21 ± 3 to 16 ± 2 ml) with no change in cardiac output, regional blood flows, and systemic vascular resistance. Finally, at 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ verapamil did not affect PR interval and dP/dt, whereas cardiac output and renal blood flow increased (from 1.9 ± 0.2 to 2.2 ± 0.2 l/min and from 102 ± 9 to 124 ± 11 ml/min, respectively), and stroke volume decreased (from 21 ± 3 to 15 ± 1 ml).

Thiopental did not affect verapamil plasma concentrations (table 2).

EXPERIMENT C

As indicated in table 3, the hemodynamic effects of thiopental were maintained for the duration of the study period.

Discussion

Our experimental preparation allows assessment of the effects of thiopental in the absence of surgical stress due

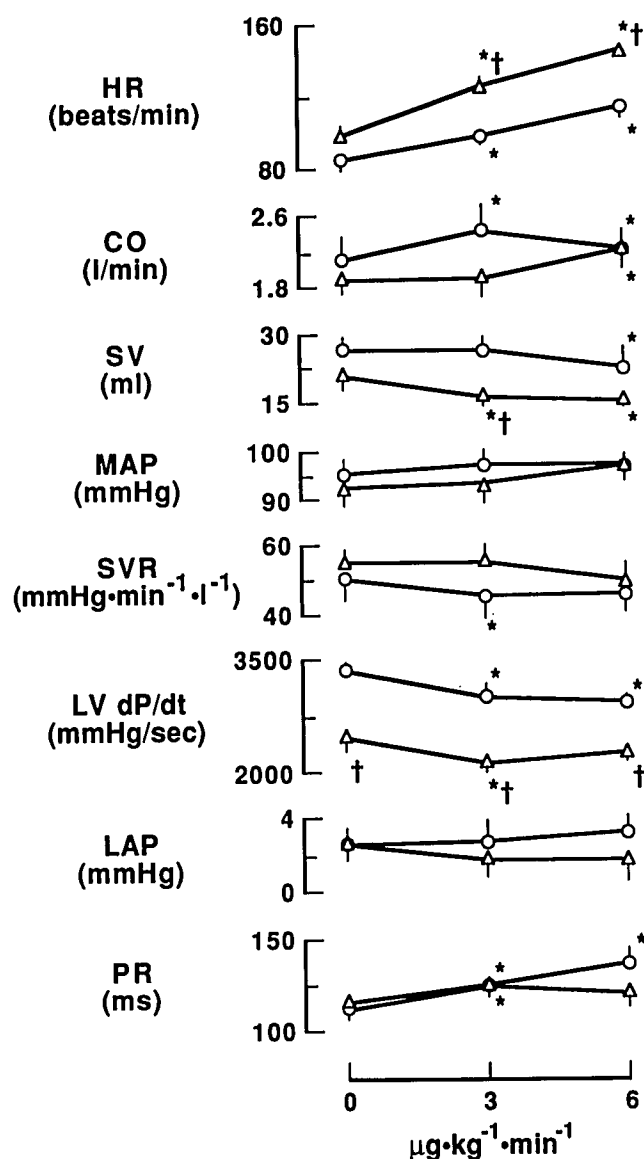


FIG. 1. Effects of two steady state infusions of verapamil (200 $\mu\text{g}/\text{kg}$ iv over 3 min followed by 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 27 min, then another 200 $\mu\text{g}/\text{kg}$ over 3 min followed by 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 27 min) on heart rate (HR), cardiac output (CO), stroke volume (SV), mean arterial pressure (MAP), systemic vascular resistance (SVR), maximum rate of rise of left ventricular pressure (LV dP/dt), left atrial pressure (LAP), and PR interval (PR) in awake (O) and thiopental-anesthetized (Δ) dogs. * $P < 0.05$ versus 0 (respective control values prior to verapamil infusions). † $P < 0.05$ awake versus thiopental at the same dose level.

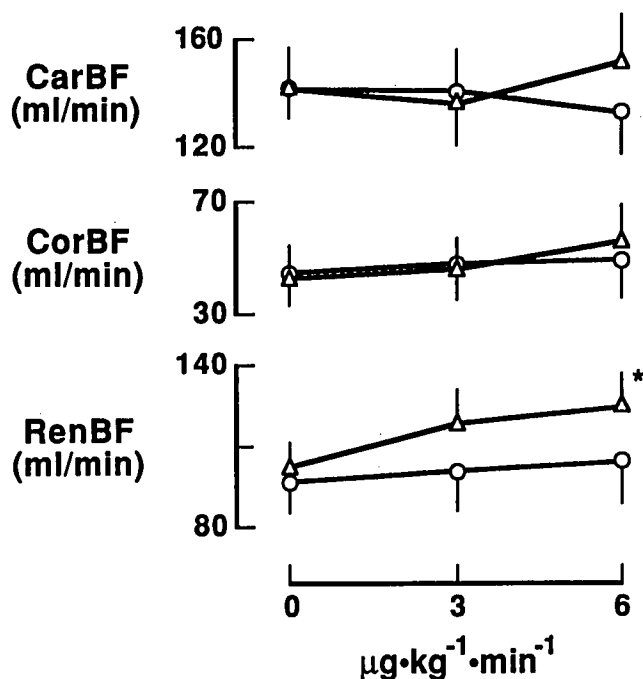


FIG. 2. Effects of two steady state infusions of verapamil (200 $\mu\text{g}/\text{kg}$ iv over 3 min followed by $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 27 min, then another 200 $\mu\text{g}/\text{kg}$ over 3 min followed by $6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 27 min) on carotid (CarBF), coronary (CorBF), and renal blood flow (ReBF) in awake (O) and thiopental-anesthetized (Δ) dogs. * $P < 0.05$ versus 0 (respective control values prior to verapamil infusion).

to acute instrumentation. Because both surgical stress and basal anesthesia can result in hemodynamic alterations, our approach provides improved experimental conditions in which to assess the role of basal anesthesia in the hemodynamic response to verapamil.

Our data demonstrate that thiopental does not affect the pharmacokinetics of verapamil but alters its pharmacodynamics. The effects of thiopental on verapamil pharmacodynamic properties were multiple but limited in magnitude. Thiopental modulated verapamil effects on heart rate and stroke volume at 3 and 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$, on systemic vascular resistance and cardiac output at 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and on PR interval, dP/dt, and renal blood flow at 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$.

Mechanisms of the verapamil-induced tachycardia include cardiac mechanoreceptor and/or baroreceptor stimulation(s) and a parasympathetic withdrawal concom-

TABLE 2. Plasma Verapamil Concentration (ng/ml)

	N	Verapamil Dose ($\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	
		3	6
Awake	9	73 \pm 6	140 \pm 14
Thiopental	9	69 \pm 6	120 \pm 12

Values are mean \pm SEM.

TABLE 3. Hemodynamic Effects of Thiopental Infusion

	N	Thiopental Control	30 min	60 min
HR (beats/min)	5	99 \pm 6	96 \pm 7	108 \pm 14
MAP (mmHg)	5	92 \pm 3	95 \pm 2	103 \pm 4
LV dP/dt (mmHg/s)	5	2,615 \pm 213	2,604 \pm 196	2,509 \pm 153
RBF (ml/min)	5	92 \pm 17	90 \pm 16	91 \pm 18
PR interval (ms)	5	116 \pm 5	120 \pm 7	114 \pm 7

Values are mean \pm SEM.

itant with a sympathetic stimulation.¹² It is unlikely that a baroreceptor stimulation was implicated because barbiturates inhibit baroreflex function.²⁰ Although verapamil has been demonstrated to centrally stimulate sympathetic outflow,²¹ the role played by the sympathetic nervous system was probably minor because barbiturates also centrally inhibit sympathetic and parasympathetic function. Our findings are of special interest because they provide evidence of an increased stimulation of ventricular mechanoreceptors *via* an increase in negative inotropic properties of verapamil during anesthesia. Yet it is established that changes in dP/dt depend not only on myocardial contractility but are also directly correlated with heart rate and afterload.²² Awake, the decrease in dP/dt induced by verapamil was associated with peripheral vasodilation and an increase in heart rate, whereas no change in systemic vascular resistance and accentuated tachycardia were recorded during anesthesia. Consequently, the same degree of direct myocardial depression should have produced a lesser reduction in dP/dt in the presence of thiopental. In contrast, at 3 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ verapamil dP/dt decreases were independent of experimental conditions and a decrease in stroke volume was recorded during anesthesia. Therefore, our findings are indicative of an accentuation of the verapamil-induced cardiac depression in the presence of thiopental.

Although in the awake state verapamil induced a dose-dependent increase in PR interval, no prolongation of PR interval was observed after raising the rate of verapamil infusion during anesthesia. PR interval is negatively correlated with heart rate. Because verapamil responses on heart rate were accentuated by the presence of thiopental, it is most likely that a heart rate-dependent decrease in PR interval counterbalanced the direct negative dromotropic properties of verapamil. However, a direct cardiac interaction between thiopental and verapamil to account for the lack of increase in PR interval cannot be ruled out.

Infusions of verapamil at 6 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ produced an increase in renal blood flow recorded only in the presence of thiopental. *In vivo*, changes in vascular tone can be direct and/or indirect. Verapamil is a direct vasodilator²³ with preferential affinity for coronary rather than renal vessels. Because the presence of thiopental did

not affect coronary circulation, it appears that the increase in renal blood flow was indirectly mediated by factors specifically implicated in the remote and/or local control of renal circulation. However, at the present time the mechanism of this interaction remains unclear.

The contribution of basal anesthesia to the negative inotropic properties of verapamil in acutely instrumented dogs appears to be limited and insufficiently explains the accentuation of the cardiac depression occurring in these dogs. Thus, consideration should be given to other factors that may also affect hemodynamic function in acutely instrumented animals.²⁴

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