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Cardiovascular Effects of and Interaction Between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs. V. Role of Pharmacokinetics and the Autonomic Nervous System in the Interactions Between Verapamil and Inhalational Anesthetics

Jacques E. Chelly, M.D., Ph.D., Einar S. Hysing, M.D.,† Douglas C. Hill, M.D.,‡ Darrell R. Abernethy, M.D., Ph.D.,§ Abdallah Dlewati, M.D.,¶ Marie-Francoise Doursout, Ph.D.,** Robert G. Merin, M.D.††*

To assess the role of both pharmacokinetics and the autonomic nervous system in the interaction between inhalational anesthetics and verapamil, dogs were chronically instrumented to measure heart rate, PR interval, dP/dt, cardiac output, and aortic blood pressure. In a first group of seven dogs, studied awake and during halothane (1.2%), enflurane (2.5%), and isoflurane anesthesia (1.6%), verapamil was infused for 30 min in doses calculated to obtain similar plasma concentrations (83 ± 10, 82 ± 6, 81 ± 10, and 77 ± 9 ng·ml^{-1}, respectively). For the latter purpose, the infusion dose was 3 and 2 μg·kg^{-1}·min^{-1} awake and during anesthesia, respectively, preceded by a loading dose of 200, 150, and 100 μg·kg^{-1}, awake, during isoflurane, and halothane and enflurane, respectively. In awake dogs, verapamil induced an increase in heart rate (24 ± 5 bpm) and PR interval (35 ± 9 msec) and a decrease in mean arterial pressure (−5 ± 2 mmHg) and dP/dt (−494 ± 116 mmHg/s). Although plasma concentrations were similar in awake and in anesthetized dogs, the only statistically significant changes induced by verapamil were an increase in heart rate and a decrease in dP/dt during halothane and enflurane, while left atrial pressure increased only with enflurane. In a second group of six dogs, verapamil pharmacokinetics were determined in the presence and absence of a ganglionic blocking drug (chlorisondamine, 2 mg·kg^{-1} iv). Blockade of ganglionic transmission resulted in a decrease in both initial volume of distribution and total clearance of verapamil —changes similar to those previously reported with inhalational anesthetics.[4] The authors' data demonstrate the importance of pharmacokinetics in the interaction between verapamil and inhalational anesthetics. Also demonstrated is the importance of autonomic nervous transmission blockade on the inhalational anesthetic-induced effects of verapamil properties. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Heart: ventricular function. Interactions: drug. Pharmacokinetics: verapamil. Pharmacology, calcium channel blocking drug: verapamil. Pharmacology, ganglionic blocking drug: chlorisondamine.)

DETERMINATION OF THE hemodynamic interactions between inhalational anesthetics and steady-state infusions of verapamil requires an experimental design which allows comparison of the effects of inhalational anesthetics during similar steady-state verapamil plasma concentrations in both conscious and anesthetized animals. Kapur *et al.*[1] previously determined the hemodynamic consequences of exposure to halothane, enflurane, and isoflurane during a wide range of verapamil plasma concentrations. Their experimental design let us compare the effects of inhalational anesthetics at similar verapamil plasma concentrations—a factor of primary importance, since we have established that inhalational anesthetics affect both the pharmacodynamics and pharmacokinetics of verapamil.[2–4] However, since the preparation used by Kapur *et al.*[1] did not permit administration of verapamil in conscious animals, the comparison of verapamil properties at the same plasma concentrations in conscious and anesthetized states remains to be established. Therefore, this study was designed to assess the hemodynamic interactions between halothane, enflurane and isoflurane, and verapamil in both conscious and anesthetized dogs. Since we previously postulated that anesthetic-induced inhibition of reflex pathways contributes to the differences in verapamil properties when infused during anesthesia as compared to awake, we decided to assess the consequences of ganglionic transmission blockade on verapamil properties.

* Associate Professor, Departments of Anesthesiology, Pharmacology and Medicine, Baylor College of Medicine.

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

‡ Research Fellow, Department of Anesthesiology, University of Texas Medical School at Houston.

§ Associate Professor, Department of Medicine, Baylor College of Medicine.

¶ Research Fellow, Department of Anesthesiology, Baylor College of Medicine.

** Senior Research Assistant, Department of Anesthesiology, 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, Baylor College of Medicine, Texas Medical Center, Houston, Texas 77030.

Methods

Instrumentation

A description of the basic model has been previously published.[2,3] Briefly, mongrel dogs weighing 16.2–24.5 kg were instrumented with the following: Tygon catheters (Tygon®, Norton Inc., Akron, OH) in the left atrium and thoracic aorta, an electromagnetic flow probe (Micron Inc.®, Los Angeles, CA) around the pulmonary artery, and a high fidelity pressure transducer (Konigsberg Inc.®, Pasadena, CA) in the left ventricular cavity. All animals were studied at least 10 days after surgery, when they were afebrile and trained to lie quietly. The details of the measurement techniques have also been previously published.[2,3] Aortic, left ventricular pressure, left atrial blood pressure, and cardiac output were continuously recorded on a Gould® polygraph (Gould Inc.®, Cleveland, OH) during the experiments. Cardiac output was measured using a Micron® RC 1000 electromagnetic flowmeter. Left ventricular dP/dt was derived electronically.

Protocol

Effects of inhalation anesthetics on cardiac responses to verapamil infusions. Seven dogs received verapamil infusions on four occasions: awake, during halothane 1.2% end tidal, during enflurane 2.5% end tidal, and isoflurane 1.6% end tidal. The order of verapamil administration was randomized; at least 3 days separated each infusion. Verapamil was infused in a dose of 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min after a loading dose of 200 $\mu g \cdot kg^{-1}$ over 3 min in conscious dogs. On the basis of anesthetic effects on verapamil pharmacokinetics,[4] and to obtain similar verapamil plasma concentrations, each dog received an infusion rate of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during anesthesia. This was preceded by a loading dose of 150 and 100 $\mu g \cdot kg^{-1}$ in the presence of isoflurane and of halothane and enflurane, respectively. Hemodynamic values and aortic blood samples for verapamil determinations were collected before and after 30 min of infusions. Anesthesia was induced by mask with nitrous oxide/oxygen and the corresponding inhalational anesthetic. When the animals were sufficiently anesthetized, the trachea was intubated, and ventilation was controlled using a Harvard ventilator (Harvard Apparatus®, So. Natick, MA) at tidal volumes of 10–15 $ml \cdot kg^{-1}$ with the rate adjusted to maintain arterial oxygen and carbon dioxide tension as in the awake animal. Immediately after tracheal intubation, nitrous oxide was discontinued and nitrogen was substituted, using a concentration which maintained arterial oxygen tension at approximately the same level as in the awake animal. By external heating if necessary, body temperature was maintained at 37° C, and was monitored by rectal thermistor probe throughout the experiment. During anesthesia, verapamil infusions were started after at least 20 min of steady-state end-tidal anesthetic concentration.

During anesthesia, end-tidal anesthetic (Beckman LB-2®, Beckman Inc., Schiller Park, IL) and carbon dioxide (Lifespan 100®, Biochem International Inc., Waukesha, WI) concentrations were continuously monitored using infrared absorption techniques. Arterial blood gas determinations were made at 20–30-min intervals during anesthesia using a Radiometer ABL® electrode system (Radiometer, Inc., Denmark). Rectal temperature was measured with a thermocouple probe (Yellow Springs Instruments®, Yellow Springs, OH). The animals were placed in a right lateral decubitus position (the same position as awake), and they received 3–5 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringers' solution during each experiment.

Effects of ganglionic transmission blockade on verapamil properties. Blockade of ganglionic transmission was obtained by injection of a ganglionic blocker, chlorisondamine 2 $mg \cdot kg^{-1}$ iv. In each dog, the accuracy of the blockade was assessed by the inhibition of the reflex tachycardia induced by nitroglycerin 30 $\mu g \cdot kg^{-1}$, iv (heart rate increased 67 ± 10 bpm before [n = 11] and 3 ± 1 bpm 30–40 min after chlorisondamine [n = 13]). Chlorisondamine was chosen for: 1) its duration of action (at least 6 h, compared to less than 2 h for hexamethonium, a ganglionic blocker of reference),[5] and 2) its absence of effects on cardiac function.[6]

Effects of ganglionic blockade and cardiac responses to verapamil infusions. Seven conscious dogs were infused with verapamil (200 $\mu g \cdot kg^{-1}$ iv over 3 min followed by 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min) in the presence and absence of chlorisondamine (45–60 min before verapamil) on two randomly assigned occasions separated by at least 3 days. Hemodynamic values and aortic blood samples were collected before and after 30 min of steady-state infusions.

Effects of ganglionic blockade and verapamil pharmacokinetics. Finally, six conscious dogs received single injections of verapamil (200 $\mu g \cdot kg^{-1}$ over 10 min) in the presence and absence of chlorisondamine (2 $mg \cdot kg^{-1}$ iv 45–60 min before verapamil), on two separate occasions. Aortic blood samples—for determination of verapamil concentrations—were collected before and 0 (end of injections), 5, 15, 30, and 45 min and 1, 2, 3, 4, and 5 h after the verapamil infusions. In addition, cardiac function was continuously recorded before, and for 60 min after, verapamil.

Sample Analysis

Blood specimens were drawn into "venoject" (Beckton-Deckinson®, Rutherford, NJ) heparinized tubes,

TABLE 1. Cardiac Effects of Similar Verapamil Plasma Concentration in Seven Dogs, Conscious and Anesthetized with Halothane, Enflurane, and Isoflurane.

	(n)	Conscious		Halothane		Enflurane		Isoflurane	
		C	V	C	V	C	V	C	V
HR bpm	7	73 ± 5	97 ± 8*	87 ± 7	99 ± 7*	91 ± 3	100 ± 3*	98 ± 7	104 ± 5
MAP mmHg	7	104 ± 5	98 ± 4*	76 ± 4	77 ± 5	66 ± 5	63 ± 4	75 ± 6	79 ± 6
CO l·min^{-1}	6	1.65 ± 0.10	1.85 ± 0.1	1.30 ± 0.1	1.22 ± 0.1	1.32 ± 0.1	1.14 ± 0.1	1.47 ± 0.1	1.46 ± 0.1
LAP mmHg	6	6.2 ± 0.8	7.5 ± 1.2	7.2 ± 1.5	7.5 ± 1.0	5.7 ± 0.5	7.8 ± 1.2*	4.7 ± 1.4	6.3 ± 1.7
dP/dt mmHg·sec^{-1}	5	2781 ± 287	2287 ± 241*	1425 ± 105	1182 ± 109*	1340 ± 133	1040 ± 107*	1530 ± 335	1571 ± 185
PR msec	7	147 ± 6	181 ± 14*	155 ± 5	167 ± 7	146 ± 7	156 ± 4	146 ± 7	147 ± 6
SVR mmHg/l/min	6	64 ± 4	54 ± 3*	61 ± 4	65 ± 5	53 ± 5	56 ± 5	51 ± 4	55 ± 4
Verap ng·ml^{-1}	7		83 ± 10		82 ± 6		81 ± 10		77 ± 9

C = control; V = verapamil; HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; LAP = left arterial pressure; dP/dt = maximum rate of rise of left ventricular pressure; PR = PR interval; SVR = systemic vascular resistance (MAP/CO); Verap = verapamil plasma concentration. Mean ± SEM.

* $P < 0.05$ *vs.* control.

centrifuged, and the plasma separated and stored at −20° C until analyzed. Concentrations of verapamil were analyzed by gas-liquid chromatography using nitrogen-phosphorous detection.[7]

Pharmacokinetic Data Analysis

Post-infusion 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,[8] the pharmacokinetic functions were used to calculate the elimination half-life, total apparent volume of distribution using the steady-state method, and total clearance.[9] In addition, central compartment volume (V_1) and the micro-rate constant—describing movement of verapamil from central to peripheral compartments (K_{12})—were determined from the pharmacokinetic function; intercompartmental clearance (Q) from the central compartment to the peripheral compartment was determined by the relationship: $Q = K_{12} \times V_1$.[10]

Data Analysis

The effects of verapamil infusions on awake and anesthetized dogs were analyzed using a one-way analysis of variance. Alpha was set at a level of 0.05. When significant, comparisons between the values recorded before and after 30 min of verapamil infusions during each experimental condition were analyzed using paired Student's *t* tests. However, for each paired comparison, the appropriate level of alpha was determined according to the Bonferroni method.[11] Data are presented as mean ± SEM.

Results

Effects of Inhalational Anesthetics on Cardiac Response to Verapamil Infusions

As indicated in table 1, our experimental design allowed us to produce similar verapamil concentrations in conscious dogs and in dogs anesthetized with halothane, enflurane, and isoflurane (table 1). In conscious dogs, verapamil increased heart rate from 73 ± 5 to 97 ± 8 bpm and PR interval from 147 ± 6 to 181 ± 14 msec, and decreased dP/dt from 2781 ± 287 to 2287 ± 241 mmHg·sec^{-1} (table 1).

Although the hemodynamic changes induced by inhalational anesthetic exposure were qualitatively the same as noted in previous studies, for a similar verapamil plasma concentration no changes were recorded during isoflurane, while only a decrease in dP/dt from 1425 ± 105 to 1182 ± 109 mmHg·sec^{-1} and an increase in heart rate from 87 ± 7 to 99 ± 7 bpm occurred during halothane. The changes produced by verapamil were the most pronounced during enflurane anesthesia. DP/dt decreased from 1340 ± 133 to 1040 ± 107 mmHg·sec^{-1}, while left atrial pressure increased from 5.7 ± 0.5 to 7.8 ± 1.2 mmHg. Simultaneously, heart rate increased from 91 ± 3 to 100 ± 3 bpm.

Effects of Ganglionic Blockade on Cardiac Response to Verapamil Infusions

After ganglionic blockade with chlorisondamine (2 mg·kg^{-1} iv), verapamil infusions resulted in a decrease in mean arterial pressure of 8 ± 2 from 97 ± 8 mmHg, dP/dt of 358 ± 107 from 2091 ± 113 mmHg·sec^{-1}, and heart rate of 11 ± 2 from 106 ± 4 bpm (table 2). In addition, verapamil plasma concentrations were higher than in control conditions (97 ± 8 *vs.* 71 ± 7 ng·ml^{-1}).

TABLE 2. Cardiac Changes Induced by Steady-state Verapamil Infusion (200 $\mu g \cdot kg^{-1}$ Bolus over 3 Min, Followed by 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 30 min) in the Presence and Absence (Control) of a Ganglionic Blocker (Chlorisondamine, 2 $mg \cdot kg^{-1}$, iv) in Six Conscious Dogs.

	(n)	Control		Chlorisondamine	
		C	V	C	V
MAP mmHg	7	103 ± 5	97 ± 8*	97 ± 8	88 ± 9*
HR bpm	7	74 ± 4	102 ± 6*	106 ± 4†	95 ± 3*
CO $l \cdot min^{-1}$	6	1.73 ± 0.1	2.12 ± 0.3	1.74 ± 0.2	1.66 ± 0.1
dP/dt $mmHg \cdot sec^{-1}$	5	2781 ± 287	2287 ± 241*	2091 ± 133†	1732 ± 206*
PR msec	7	144 ± 7	178 ± 15*	134 ± 6	178 ± 7*
SVR mmHg/l/min	6	61 ± 5	49 ± 6*	58 ± 9	55 ± 9

C = control; V = verapamil; HR = heart rate; MAP = mean arterial pressure; CO = cardiac output; dP/dt = maximum rate of rise of left ventricular pressure; PR = PR interval; SVR = systemic vascular resistance (MAP/CO). Mean ± SEM.
* = $P < 0.05$ *vs.* C.
† = $P < 0.05$ *vs.* control.

EFFECTS OF GANGLIONIC BLOCKADE ON VERAPAMIL PHARMACOKINETICS

A representative set of verapamil plasma concentration time-curves (after 200 $\mu g \cdot kg^{-1}$ iv over 10 min) in the same dog in the presence and absence of a ganglionic blocker chlorisondamine (2 $mg \cdot kg^{-1}$ iv) is shown in figure 1. Blockade of ganglionic transmission was associated with a decrease in initial volume of distribution and total clearance of verapamil (table 3).

Discussion

We have previously demonstrated that the effects of steady-state infusions of verapamil on cardiac function are more pronounced in dogs anesthetized with halothane, enflurane, or isoflurane than in conscious dogs.[2,3] In addition, we have documented that, following a given dose of verapamil, plasma concentrations are higher in anesthetized than in awake animals, suggesting that inhalational anesthetics affect verapamil pharmacokinetics. We further demonstrated that steady-state volume of distribution and total clearance of verapamil are decreased during anesthesia with halothane, enflurane, and isoflurane.[4] In other words, both the pharmacodynamics and pharmacokinetics of verapamil are affected by concomitant administration of volatile anesthetics.

In this study, the animals involved were more sensitive to drugs, since the cardiac effects induced by both inhalational anesthetics and verapamil were more pronounced than those previously reported when using the same experimental design.[2,3] Despite this higher sensitivity, hemodynamic interactions between inhalational anesthetics and verapamil were minimal when verapamil plasma concentrations were similar in the awake and in the anesthetized state. In the present study, decreased loading doses and infusion rates were required to generate verapamil plasma concentrations similar to those obtained awake. As previously reported by Kapur *et al.*,[1] we observed that verapamil produced minimal changes with isoflurane, while the response was moder-

TABLE 3. Effect of Chlorisondamine (2 mg · kg^{-1} iv) on Single-dose Verapamil (200 $\mu g \cdot kg^{-1}$ iv over 10 min) Pharmacokinetics in Six Conscious Dogs.

	Verapamil	Verapamil + Chlorisondamine
Initial volume of distribution (l)	40 ± 4	30 ± 2*
Intercompartmental clearance ($l \cdot h^{-1}$)	211 ± 36	175 ± 44
Volume of distribution at steady-state (l)	101 ± 17	78 ± 10
Total clearance ($l \cdot h^{-1}$)	54 ± 6	35 ± 4*
Elimination half-life (h)	1.64 ± 0.27	1.91 ± 0.29

Mean ± SEM.
* $P < 0.05$ *vs.* verapamil.

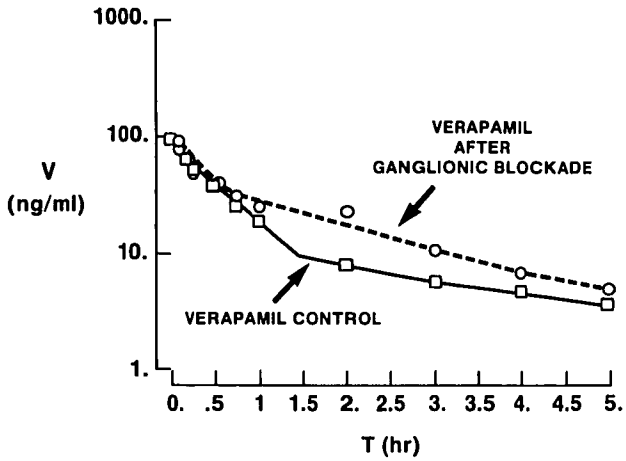

FIG. 1. A representative set of verapamil plasma concentration time-curves after injections of 200 $\mu g \cdot kg^{-1}$ over 10 min in the same dog studied in the presence and absence of a ganglionic blocker (chlorisondamine, 2 $mg \cdot kg^{-1}$ iv).

ate with halothane, and most pronounced with enflurane.

Our study provides experimental evidence that inhalational, anesthetic-induced inhibition of the reflex pathway plays a dominant role in the cardiac interactions between verapamil and inhalational anesthetics.[2,3] We recorded a similar decrease in dP/dt during verapamil infusions in conscious dogs pretreated with chlorisondamine and in dogs anesthetized with enflurane and halothane. In addition, in the presence of ganglionic blockade, verapamil plasma concentration was increased during infusions. Although both the volume of distribution and total clearance of verapamil recorded after single-dose injections were decreased, the increased verapamil plasma concentration noted during infusions was most likely related to the ganglionic blockade-induced decrease in verapamil total clearance, since plasma concentrations are clearance-dependent and volume-independent. More importantly, the effects of chlorisondamine on verapamil distribution and elimination constitute important evidence of the contribution of ganglionic blockade as a mechanism of the previously reported[4] pharmacokinetic interactions between verapamil and inhalational anesthetics. In addition to decreased total clearance, a decrease in verapamil initial volume of distribution was also noted during inhalational anesthetic exposure. For high clearance drugs like verapamil, a decrease in total clearance is suggestive of a decrease in hepatic blood flow. Hamann *et al.*[12] introduced the concept that the sympathetic nervous system may modulate verapamil elimination. They demonstrated that, in the presence of propranolol, verapamil clearance was reduced because of a decrease in hepatic blood flow, which itself was related to a decrease in cardiac output in thiopental-anesthetized dogs. During halothane and enflurane, cardiac output decreased, but, during isoflurane and in the presence of chlorisondamine, no changes in cardiac output were recorded. Moreover, we demonstrated earlier that halothane, enflurane, and isoflurane induced a decrease in verapamil total clearance,[4] while Gelman *et al.*[13] and Hughes *et al.*[14] demonstrated that halothane and enflurane, but not isoflurane, reduced total hepatic blood flow. Therefore, the relationship between cardiac output, hepatic blood flow, and verapamil elimination remains to be established. It is possible that the effects of inhalational anesthetics on verapamil elimination represent the consequence of depression of both hepatic blood flow and hepatic metabolic capacity, as demonstrated by the effects of halothane on propranolol elimination.[15] According to this hypothesis, in the presence of inhalational anesthetics, hepatic drug extraction is sufficiently impaired for high clearance drugs to become drugs of moderate and even low extraction. In these conditions, drug elimination becomes dependent on the liver metabolic capacity, which is inhibited by inhalational anesthetics.[16,17] In the absence of convincing evidence of the interactions between calcium channel blocking drugs and inhalational anesthetics at the site of calcium movement through voltage-dependent calcium channels,[18] our data suggest that accentuation of the direct cardiac response, recorded after verapamil injections, is dependent upon the effects of inhalational anesthetics on verapamil disposition. It is more likely that the anesthetic-induced decrease in verapamil clearance is the important mechanism when considering the interactions recorded during verapamil infusions. However, with single injections of verapamil, anesthetic-induced decreases in both volume of distribution and clearance contribute to the effect recorded. Our study demonstrates that changes in drug disposition and alterations of the function of the autonomic nervous system play a major role in the cardiac response to verapamil. However, other factors seem to be involved. Previous reports have demonstrated that the dose of verapamil,[1] speed of injections, concentration of inhalational anesthetics,[2,3] and existence of a myocardial depression[19] represent factors which also modulate the cardiac response to verapamil.

Our data, especially when combined with our previous findings, demonstrate the importance of pharmacokinetics in the pharmacological interaction between verapamil and inhalational anesthetics. This study also provides experimental evidence of ganglionic transmission blockade as a mechanism for the inhalational anesthetic-induced alteration of verapamil properties.

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