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Effects of Inhalational Anesthetics on Verapamil Pharmacokinetics in Dogs

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Six dogs were chronically instrumented in order to collect aortic blood samples and record mean arterial pressure, cardiac output and heart rate. Each animal received verapamil 200 $\mu g \cdot kg^{-1}$ by 10-min intravenous infusions on four occasions in random sequence: awake, and during halothane 1.2%, enflurane 2.5%, and isoflurane 1.6% anesthesia. Rate of initial distribution of verapamil was reduced during anesthetic exposure. Verapamil intercompartmental clearance from the central compartment to the peripheral compartment was decreased during exposure to halothane and isoflurane, and tended to decrease during enflurane exposure as well. Verapamil terminal volume of distribution at steady-state was reduced by halothane, enflurane, and isoflurane exposure as compared with awake: 65 ± 10, 80 ± 9, and 93 ± 19 l, respectively, *versus* 132 ± 12 l (mean ± SEM; $P < 0.05$). Verapamil total clearance was also reduced by halothane, enflurane, and isoflurane as compared with awake: 37 ± 4, 39 ± 2 and 41 ± 3 $l \cdot h^{-1}$, respectively, *versus* 64 ± 7 $l \cdot h^{-1}$ ($P < 0.05$). Verapamil administered to awake animals resulted in a decrease from baseline in mean arterial pressure; 95 ± 8 mmHg *versus* 108 ± 4 mmHg ($P < 0.05$): and an increase in cardiac output; 2.60 ± 0.33 $l \cdot min^{-1}$ *versus* 1.93 ± 0.22 $l \cdot min^{-1}$ ($P < 0.05$). During halothane, enflurane, and isoflurane anesthesia, verapamil administration resulted in a similar decrease in mean arterial pressure; however cardiac output decreased, in contrast to the increase noted in awake animals. This study suggests that the pharmacokinetic drug–drug interactions may contribute to pharmacodynamic interactions between verapamil and inhalational anesthetics. Our data also indicate that increased plasma concentrations after a single verapamil dose may occur due to decreased intercompartmental clearance, and to a lesser extent increased initial volume of distribution and decreased apparent volume of distribution. (Key words: Anesthetics, volatile: enflurane; halothane; isoflurane. Ions. Pharmacokinetics. Pharmacology: calcium channel blocker; verapamil.)

PREVIOUSLY WE HAVE demonstrated that the inhalational anesthetics, halothane, isoflurane, and enflurane, interact with the calcium blocker drug, verapamil, to enhance its effects on cardiac conduction, mean arterial pressure, and left ventricular contractility in dogs.[1,2] It is established that the inhalational anesthetics may interfere with calcium movement across cell membranes and consequently alter physiologic processes that are mediated by transmembrane calcium movements,[3] suggesting that pharmacodynamic interactions between calcium channel blockers and inhalational anesthetics may be expected. However, from our studies, it was unclear whether the interaction between verapamil and inhalational anesthetics was purely dynamic, or kinetic with pharmacodynamic consequences, because halothane, isoflurane, and enflurane exposure each resulted in an increased steady-state verapamil plasma concentration at the time the increased pharmacodynamic effects were demonstrated.[1,2]

The aim of this study was to determine the nature of the pharmacokinetic interactions between verapamil and the inhalational anesthetics halothane, isoflurane, and enflurane.

Methods

Six heartworm-free, mongrel dogs weighing between 14.7 and 27.1 kg (mean 21.6) were instrumented under halothane anesthesia. After a left thoracotomy, a Tygon® (Norton, Inc., Akron, OH) catheter was placed in the thoracic aorta through the left subclavian artery and an electromagnetic flow probe (14–16 mm, Micron, Inc., Los Angeles, CA) was placed around the pulmonary artery. The catheter and flow probe leads were tunneled subcutaneously to a common exit point just caudad to the skull on the dorsum of the animal's neck. Ampicillin and streptomycin were administered before surgery and for 5 days following surgery. Dogs were permitted to recover from surgery for at least 10 days, during which time they were trained to lie quietly.

Each dog underwent four separate trials, separated by at least 3 days and randomly ordered:

Trial I. Verapamil 200 $\mu g \cdot kg^{-1}$ by 10-min intravenous infusion *via* glass syringe.

Trial II. Verapamil as in Trial I—dog anesthetized with halothane 1.2%.

Trial III. Verapamil as in Trial I—dog anesthetized with isoflurane 1.6%.

Trial IV. Verapamil as in Trial I—dog anesthetized with enflurane 2.5%.

On the day of each experiment, an intravenous catheter was placed in a fore or hind leg vein and lactated Ringer's

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solution infused at 3–5 ml · kg^{-1} · h^{-1} for the duration of the experiment. Continuous low-speed polygraph recordings (25 mm · m^{-1}) were made of mean aortic pressures, heart rate, and cardiac output.

During experiments using anesthesia, the animals were prepared in the same fashion as for awake experiments. Anesthesia was then induced by mask with nitrous oxide–oxygen and the appropriate anesthetic. When the animals were sufficiently anesthetized, the trachea was intubated and ventilation was controlled using a Harvard ventilator at tidal volumes of 10–15 ml · kg^{-1} with the rate adjusted to maintain end-tidal carbon dioxide concentration equal to that in the awake animal. Immediately after tracheal intubation, nitrous oxide was discontinued and nitrogen was substituted in a concentration that maintained arterial oxygen tension at approximately the same level as in the awake animal.[1] The end-tidal anesthetic concentration was maintained at 1.2%, 1.6%, and 2.5% for halothane, isoflurane, and enflurane, respectively. These anesthetic concentrations were chosen because: 1) they are within the range of clinical doses; 2) they produce similar decreases in mean arterial pressure; and 3) they are the doses used in the previous studies where we demonstrated that inhalational anesthetic exposure resulted in an increase in verapamil plasma concentration. Core body temperature was maintained at 37° C throughout the experiment by external heating with a heating blanket, if necessary, and monitored by rectal thermometer.

Measurement Techniques

Aortic pressure was transduced with Gould Statham P50® strain gauges (Cleveland, OH), which were zeroed and calibrated against a mercury manometer before each experiment. Cardiac output was measured using a RC 1000® Micron electromagnetic flow meter (Micron, Inc.). Cardiac output was zeroed to the flow recorded during the end of diastole, and the gain for each flow probe was calibrated before each experiment. Arterial blood gas determinations were made at intervals during the various phases of the experiments using a radiometer ABL electrode system. During anesthesia, airway anesthetic (Beckman LB-2®, Beckman Instruments, Inc., Schiller Park, IL) and carbon dioxide concentrations (Lifespan 100®, Biochem International, Inc., Waukesha, WI) were continually monitored using infrared absorption techniques. Rectal temperature was measured with a thermocouple probe (Yellow Springs Instruments, Inc., Yellow Springs, OH).

Aortic blood samples were drawn into Venoject® (Beckton-Dickinson, Rutherford, NJ) heparinized tubes before administration of verapamil; at the end of the infusion; at 5, 15, 30, and 45 min; and 1, 2, 3, 4, and 5 h. Blood specimens were centrifuged and the plasma separated and stored at −20° C until analyzed.

Sample Analysis

Concentrations of verapamil and norverapamil were analyzed by gas–liquid chromatography using nitrogen–phosphorous detection.[4] Binding of verapamil to plasma proteins was determined by equilibrium dialysis with duplicate 1-ml plasma samples.[5] Plasma samples for dialysis experiments were obtained during anesthesia 4–6 h after verapamil administration. Verapamil concentrations from the administered verapamil were less than 20 ng · ml^{-1}, and norverapamil was undetectable in these samples. Plasma samples were spiked with verapamil 200 ng · ml^{-1}. This was achieved by adding 30 μl of verapamil (20 μg · ml^{-1}) dissolved in methanol to a clean tube. Methanol was evaporated at room temperature under a stream of nitrogen. Three milliliters of plasma was then added to the tube and the tube vortexed vigorously, allowed to stand 15 min, and then again vortexed. From this solution, duplicate 1-ml plasma samples were obtained and then placed in dialysis membrane tubing (Spectrapore® cellulose tubing, molecular weight cut off 12,000 to 14,000; Fisher Scientific, Pittsburgh, PA). Each sample was dialyzed against 8 ml of 0.1 M phosphate buffer, *p*H 7.4 at 37° C for 5 h. In previous experiments, the binding equilibrium was shown to be reached at 4 h, and verapamil binding was concentration-independent over a range of 100–5,000 ng · ml^{-1}. The concentration of verapamil in dialyzed plasma and dialysate was determined as described earlier. Postdialysis verapamil concentrations were 160–170 ng · ml^{-1} in the dialysate. Recovery of verapamil from the system was determined in previous experiments to be 98 ± 2%. The percent of unbound verapamil free fraction was then calculated by dividing the dialysate concentration by the dialyzed plasma concentration and multiplying the result by 100. Recovery from the dialysis system was complete, and variation between duplicate samples was less than 10%.

Pharmacokinetic Data Analysis

After intravenous 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 Drug Model in the PROPHET network. After correction of the coefficients for the infusion time,[6] the derived functions were used to calculate the elimination half-life, total apparent volume of distribution using the steady-state method, and total clearance.[7] In addition, estimation of central compartment volume (V_1), micro-rate constant describing movement of verapamil from central to peripheral compartment (K_{12}), and intercompartmental clearance

** Holdford NHG: Drug model, Public Proceedings Notebook. Edited by Perry HM. Massachusetts, Bolt, Beranch, and Newman, 1982.

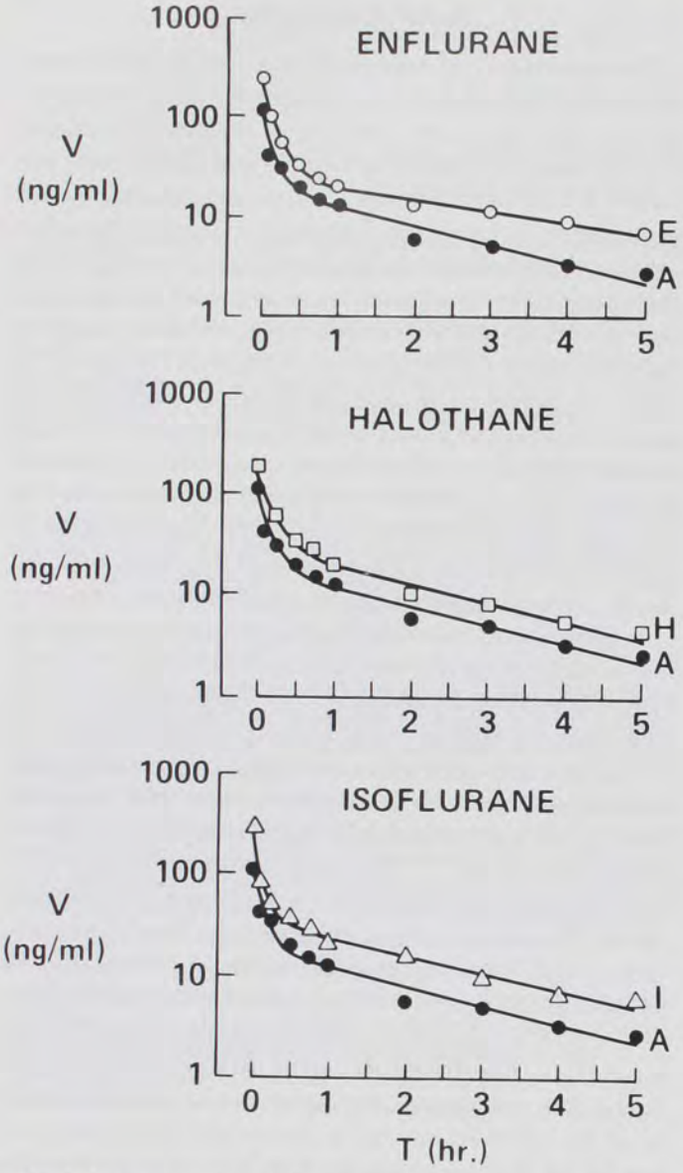

FIG. 1. A representative set of verapamil plasma concentration-time curves after injection of 200 $\mu g \cdot kg^{-1}$ over 10 min in the same dog studied awake and during enflurane, halothane, and isoflurane anesthesia. V = verapamil plasma concentration; A = awake; H = halothane; I = isoflurane; E = enflurane.

(Q) from the central compartment to the peripheral compartment were made by the relationship: $Q = K_{12} \cdot V_1$.[8]

Differences in derived pharmacokinetic parameters and pharmacodynamic variables were analyzed by a repeated measure analysis of variance. When significant, multiple paired comparisons were applied. Alpha was set up at a level of 0.05. However, for each paired comparison, the appropriate level of alpha was determined according to the Bonferroni method.[9] Data are presented as mean ± SEM.

Results

Pharmacokinetics

A representative set of verapamil plasma concentration-time curves after verapamil administration in the same dog studied awake and during enflurane, halothane, and isoflurane anesthesia is shown in figure 1. Compared with awake values, the initial volume of distribution of verapamil decreased during exposure to halothane and tended to decrease during enflurane and isoflurane. In addition, the calculated verapamil intercompartmental clearance was decreased during exposure to halothane and isoflurane, and tended to decrease during enflurane exposure (table 1). Apparent terminal volume of distribution of verapamil during isoflurane, enflurane, and halothane anesthesia was significantly decreased (fig. 2; table 1), as was verapamil total clearance during each of the anesthetic exposures (fig. 2; table 1). Therefore, the elimination half-life of verapamil remained essentially unchanged (table 1). Between-group comparisons for each of the anesthetics indicated there were no significant differences between respective agents for intercompartmental clearance, volume of distribution, and total clearance. Finally the free fraction of verapamil during each of the trials was not different (table 1); therefore, alterations in protein binding cannot be invoked to explain the observed pharmacokinetic interaction.

Pharmacodynamics

Hemodynamic values recorded before and at the maximum deviation from baseline during verapamil infusion in dogs conscious and anesthetized with isoflurane, enflurane, and halothane are shown in table 2. Isoflurane, enflurane, and halothane exposure each resulted in a sim-

TABLE 1. Effects of Inhalational Anesthetics on Verapamil Pharmacokinetics (mean ± SEM)

	Awake	Isoflurane	Enflurane	Halothane
Initial volume of distribution (l)	31.4 ± 2.9	25.1 ± 7.6	19.8 ± 2.0†	15.7 ± 2.6*
Intercompartmental clearance ($l \cdot min^{-1}$)	301 ± 44	178 ± 31*	195 ± 17	141 ± 25*
Elimination half-life (h)	1.78 ± 0.07	1.95 ± 0.30	1.72 ± 0.20	1.56 ± 0.12
Volume of distribution at steady-state (l)	132 ± 12	93 ± 19*	80 ± 9*	65 ± 10*
Total clearance ($l \cdot h^{-1}$)	64 ± 7	41 ± 3*	39 ± 2*	37 ± 4*
Free fraction (% not bound to plasma protein)	7.6 ± 1.6	6.5 ± 1.2	8.2 ± 1.5	9.3 ± 1.6

* $P < 0.05$ *vs.* awake.

† $P = 0.05$ *vs.* awake.

ilar decrease in mean arterial pressure and an increase in heart rate as compared with the awake state. Cardiac output values, compared with values recorded during the awake state, were decreased only during enflurane anesthesia. In the conscious state, verapamil induced a decrease in mean arterial pressure, an increase in heart rate, and an increase in cardiac output. Verapamil infused during halothane anesthesia produced a decrease in mean arterial pressure, an increase in heart rate, and a decrease in cardiac output when compared with halothane preinfusion values (table 2). During isoflurane and enflurane anesthesia, verapamil infusions, when compared with isoflurane or enflurane preinfusion values (table 2), produced similar changes to those recorded during halothane anesthesia, except that the increase in heart rate did not reach statistical significance during enflurane anesthesia. Despite the differences in the hemodynamic effects of verapamil infused awake and during halothane, enflurane, and isoflurane exposure, in all cases the maximum changes produced by verapamil were recorded 7–8 min after the beginning of infusion, and after 15–30 min, hemodynamic variables returned to control.

Discussion

Verapamil initial volume of distribution and intercompartmental clearance decreased during halothane and isoflurane exposure, and tended to decrease during enflurane. This initial decreased rate of verapamil transfer from central to peripheral compartments in the presence of a decreased initial volume of distribution during exposure to inhalational anesthetics may account in part for the decrease in cardiac output after verapamil instead of the increase noted in awake animals. This initial impairment in transfer of verapamil out of the central compartment may be particularly important in our experimental conditions because verapamil produced only transient hemodynamic changes during the early phase of drug distribution. Hamann *et al.*[10] demonstrated that although cardiac output was increased in the presence of low verapamil concentration, it was progressively decreased with increasing concentrations of verapamil. In the present experiment, high concentrations of verapamil remain in the central compartment for a prolonged time during anesthetic exposure as a result of the decreased rate of distribution into the peripheral compartment. However, it is also possible that the verapamil-induced decrease in cardiac output during anesthesia is related to the anesthetic-induced inhibition of reflexes. In awake dogs the increase in cardiac output produced by verapamil is dependent on baroreflex-mediated sympathetic stimulation and parasympathetic withdrawal as a result of hypotension,[11,12] and inhalational anesthetics inhibit the baroreflex pathways.[13,14]

Verapamil total clearance was also decreased in dogs breathing inhalational anesthetics. For drugs like verapamil[15] with high hepatic extraction, hepatic blood flow

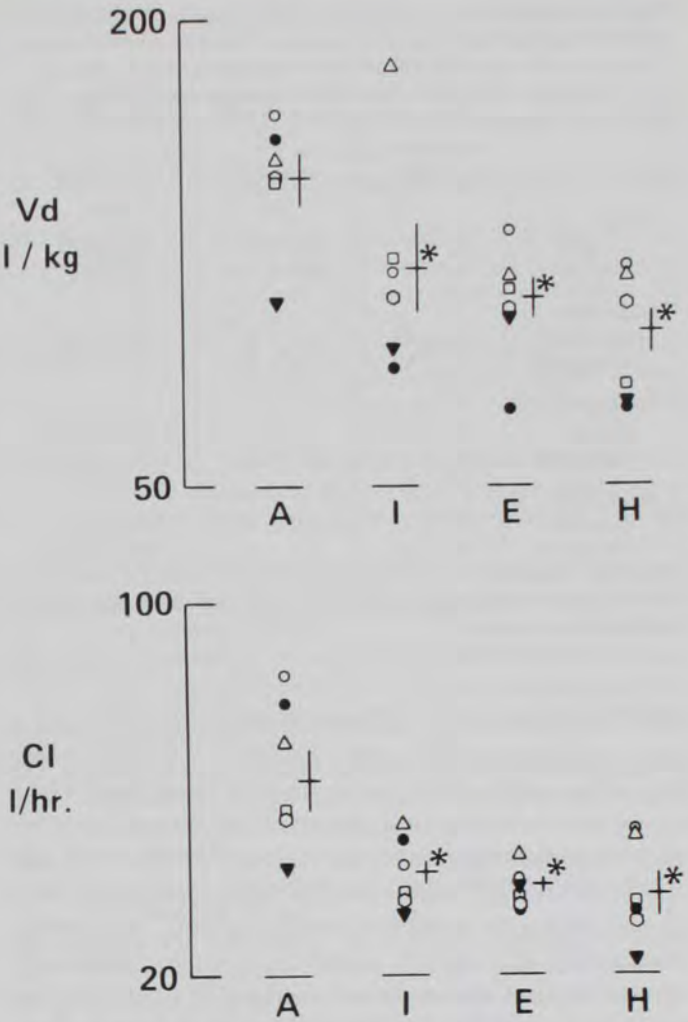

FIG. 2. Effects of isoflurane (I), enflurane (E), and halothane (H) on volume of distribution (Vd) (*upper*) and verapamil total clearance (Cl) (*lower*). Each symbol represents one dog, and the bars represent mean ± SEM. *$P < 0.05$ *vs.* awake (A).

rather than intrinsic hepatic drug-metabolizing capacity[16] is the primary determinant of clearance, and an anesthetic-induced decrease in hepatic blood flow may be predicted to result in decreased drug clearance. Inhalational anesthetics affect hepatic blood flow differently, depending upon the agent. Halothane and enflurane induce a dose-dependent decrease in the hepatic arterial blood flow, whereas isoflurane increases it.[17] However, they all induce a dose-dependent decrease in the portal blood flow.[17,18] Gugler *et al.*[19] demonstrated that clearance of lidocaine, a prototype high-clearance drug, was reduced by a portocaval shunt. Many subsequent studies have demonstrated decreased clearance of high-clearance drugs in hepatic disease states, such as cirrhosis, in which extensive portosystemic shunting may occur, although in this instance decreased drug metabolism may also play a role.[20] Similar findings have been reported for verapamil.[21–23] Therefore, anesthetic-induced decreases in hepatic blood flow could explain, at least in part, the decreased verapamil clearance noted in this study. However, the most

TABLE 2. Maximum Changes Produced by Verapamil (200 $\mu g \cdot kg^{-1}$ over 10 min) on Mean Arterial Pressure, Heart Rate, and Cardiac Output in the Same Dog Studied Awake and during Isoflurane, Enflurane, and Halothane Anesthesia (mean ± SEM).

	Mean Arterial Pressure	Heart Rate	Cardiac Output
Awake			
Control	108 ± 4	80 ± 6	1.93 ± 0.22
Verapamil	95 ± 8†	120 ± 14†	2.6 ± 0.33†
Isoflurane			
Control	76 ± 6*	106 ± 5*	1.96 ± 0.26
Verapamil	66 ± 6†	118 ± 12†	1.75 ± 0.21†
Enflurane			
Control	71 ± 10*	94 ± 9*	1.63 ± 0.15*
Verapamil	61 ± 11†	111 ± 7	1.32 ± 0.07†
Halothane			
Control	77 ± 4*	108 ± 9*	1.80 ± 0.18
Verapamil	66 ± 2†	121 ± 9†	1.53 ± 0.22†

* $P < 0.05$ awake control *vs.* isoflurane control, enflurane control, and halothane control.
† $P < 0.05$ *vs.* control.

likely explanation for decreased verapamil clearance is the combined inhibition of the hepatic oxidative biotransformation and a reduction in hepatic blood flow. Halothane has previously been shown to inhibit oxidative hepatic biotransformation of aminopyrine,[24] fentanyl,†† and d,l propranolol.[25] Isoflurane has been reported to have similar effects on aminopyrine elimination,[24] and enflurane inhibits aminopyrine metabolism *in vitro*,[26] although no *in vivo* effect has been demonstrated.[24] Therefore, hepatic drug oxidation can certainly be impaired by these agents. However, supporting the concept that both alteration in hepatic blood flow and hepatic drug-oxidizing capacity play a role in the observed interaction, halothane has been reported to reduce clearance of lidocaine in humans[27] and propranolol in dogs.[25] In the latter study, indirect measurement of hepatic blood flow and metabolic ability showed a 26% reduction in hepatic blood flow, while intrinsic propranolol clearance (liver) decreased by 62%. These workers reported only a decrease in systemic clearance with no change in volume of distribution of propranolol.[25]

In the absence of an alteration of verapamil binding to plasma proteins, the decrease in the terminal apparent volume of distribution that occurred with the inhalational anesthetics suggests decreased distribution following distribution–redistribution processes into the peripheral compartment. Verapamil is known to distribute extensively into extravascular tissue compartments, most notably the lung, liver, kidney, and heart, with lower tissue concentration in skeletal muscle, brain, and adipose tissue.[5] Therefore, a postulated mechanism for decreased apparent terminal distribution is an anesthetic-induced impairment in the capacity of some or all of these tissues to serve as peripheral distribution sites for verapamil. We cannot directly address that postulate with the present data. Hemodynamic alterations induced by the inhalational anesthetics may also contribute to the reduction in the verapamil volume of distribution, either directly or by the regional blood-flow redistribution that these agents produce. Thomson *et al.*[28] demonstrated that congestive heart failure, which results in such redistribution of blood flow, is associated with decreased volume of distribution of another high-clearance drug, lidocaine. Inhalational-anesthetic–induced myocardial depression is well documented *in vitro* and *in vivo*, especially for halothane[29] and enflurane,[30] and is demonstrated in this study as well (table 2). Isoflurane effects on cardiac function are generally considered to be the balance among direct negative inotropic effects, peripheral vasodilation, and the resulting decrease in afterload that results in the maintenance of cardiac output *in vivo*.[31] Redistribution of blood flow during exposure to volatile anesthetics from tissues with high verapamil binding ability, like the lung, heart, and liver, to tissues with lower verapamil binding ability, like skeletal muscle and skin, has been documented.[32–35] Finally, a potential mechanism by which inhalational anesthetic hemodynamic properties may also contribute to the decrease in the apparent volume of distribution of verapamil is their effects on arteriovenous shunting across the pulmonary and other capillary beds. Despite their effects on cardiac output, halothane and isoflurane increase arteriovenous shunting as demonstrated by microsphere technique, which consequently may result in decreased tissue perfusion and uptake of drugs.[35] Further studies directly evaluating verapamil peripheral tissue binding in the presence of volatile anesthetics will be required to establish the role of tissue distribution for this *in vivo* pharmacokinetic–pharmacodynamic drug–drug interaction.

In conclusion, a drug–drug interaction having potential clinical importance was demonstrated between three inhalational anesthetics and verapamil. Decreased drug clearance during exposure to these volatile anesthetics may result in reduction of the verapamil dose required to achieve therapeutic plasma verapamil concentrations during infusion. Perhaps more importantly, large increases in verapamil plasma concentrations after a single verapamil dose may occur due to decreases in verapamil intercompartmental clearance and, to a lesser extent, increased initial volume of distribution and decreased apparent volume of distribution.

†† Borel JD, Bentley JB, Nenade RE Jr, Gillespie TJ: The influence of halothane on fentanyl pharmacokinetics (abstract). ANESTHESIOLOGY 57:A239, 1982.

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