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Cardiovascular Effects of and Interaction Between Calcium Blocking Drugs and Anesthetics in Chronically Instrumented Dogs. VI. Verapamil and Fentanyl-pancuronium

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To assess the interaction between verapamil and fentanyl-pancuronium, dogs were chronically instrumented to measure heart rate; PR interval; aortic, left ventricular, and left atrial pressures; and coronary, carotid, and renal blood flows. The effect of fentanyl citrate infusion on single-dose verapamil pharmacokinetics was examined in six animals. The effects of verapamil infusion (3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were examined in the conscious state and during fentanyl infusion plus pancuronium on two separate occasions in nine dogs. In addition, the effects of fentanyl citrate (500 $\mu g \cdot kg^{-1}$ followed by 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) were examined over 1 h of infusion. Fentanyl infusion did not affect single-dose verapamil pharmacokinetics. In the conscious animals, verapamil increased heart rate and PR interval, and slightly decreased LV dP/dt. Fentanyl combined with pancuronium increased mean arterial pressure and LV dP/dt. During fentanyl infusion, verapamil decreased mean arterial pressure and LV dP/dt, increased PR interval, and did not change heart rate. The hemodynamic effects of fentanyl infusion were steady over 1 h. In contrast to the inhalational anesthetics, which alter verapamil pharmacokinetics and have mainly additive effects with verapamil on left ventricular contractility, cardiac conduction, and regional blood flows, fentanyl-pancuronium had no effect on verapamil pharmacokinetics and minimal effect on verapamil pharmacodynamics in healthy dogs. (Key words: Anesthetics, intravenous: fentanyl. Heart: ventricular function. Interactions: drug. Pharmacokinetics: verapamil. Pharmacology, calcium channel blocking drug: verapamil.)

IT HAS PREVIOUSLY been demonstrated that the cardiovascular interactions between calcium channel blocking drugs and anesthetics are dependent upon both pharmacokinetic and pharmacodynamic interactions.[1–3] High-dose fentanyl anesthesia, up to 150 $\mu g \cdot kg^{-1}$, has been advocated for patients with cardiovascular disease, particularly those with decreased cardiac reserve.[4] Verapamil may be indicated in many of these same surgical patients for treatment of supraventricular arrhythmias, hypertension, or myocardial ischemia. Therefore, documenting the cardiovascular interactions between verapamil and fentanyl is important. A previous clinical study involving a population of patients receiving beta adrenergic blocking drugs, nitrates, and nifedipine examined the hemodynamic effects of verapamil after large doses of fentanyl.[5] However, beta blocking drugs have been demonstrated to interact with nifedipine[6] and verapamil.[7] This study assessed the effects of fentanyl and pancuronium on verapamil pharmacokinetics. We also examined the effects of verapamil and fentanyl-pancuronium alone, and in combination, on the cardiovascular system of conscious, chronically instrumented dogs.

Materials and Methods

Instrumentation

Details of the basic model have been previously published.[1] Briefly, nine healthy dogs, free of heart worms and weighing an average of 19.8 ± 1.5 kg (SEM), were instrumented as follows: Tygon® catheters (Tygon, Norton, Inc., Akron, OH) in the left atrium and thoracic aorta; pulsed Doppler flow probes (Baylor College of Medicine, Houston, TX) around the circumflex coronary, left common carotid, and left renal arteries; an electromagnetic flow probe (Micron Inc.®, Los Angeles, CA) around the pulmonary artery; and a high-fidelity pressure transducer (Konigsberg Inc.®, Los Angeles, 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 on their right sides. Periodic blood counts demonstrated that the dogs maintained their hematocrits throughout the study period. Details of the measurement techniques have been previously described.[1] Doppler flow probes were calibrated

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in terms of frequency shifts. Aortic, left ventricular, and left atrial pressures; cardiac output; and carotid, coronary, and renal blood flows 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.

PROTOCOLS

Effect of Fentanyl Infusion on the Pharmacokinetics of Single-dose Verapamil. The pharmacokinetics of single injections of verapamil in the conscious animal and during infusion of fentanyl (and paralysis with pancuronium) were studied on two separate occasions in six dogs. Experiments were separated by at least 4 days, and the order was randomly assigned.

Experiment I. Verapamil was injected in a dose of 200 $\mu g \cdot kg^{-1}$ over 10 min. Aortic blood samples (3 ml) were collected prior to and 1, 3, 5, 10, 15, 30, and 45 min after, and 1, 2, 3, 4, and 5 h after verapamil. In addition, cardiac function was continuously recorded before and for 60 min after verapamil.

Experiment II. After conscious hemodynamic measurement, animals received fentanyl citrate 500 $\mu g \cdot kg^{-1}$ followed by 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for the remainder of the experiment, and pancuronium 0.1 $mg \cdot kg^{-1}$ followed by intermittent 0.02 $mg \cdot kg^{-1}$ doses as needed. Fentanyl dosing was based on the findings of two studies that investigated the anesthetic properties of fentanyl in dogs.[8,9] Bailey *et al.* reported that the anesthetic ED_{50} for fentanyl citrate 5 min after administration of a single bolus was 329 $\mu g \cdot kg^{-1}$ in untrained dogs.[8] In addition, Arndt *et al.* have reported the effects of five separate fentanyl injections to a cumulative dose of 165.7 $\mu g \cdot kg^{-1}$ administered over 20 min in trained dogs. Fentanyl abolished all heart rate and blood pressure increases in response to tail clamping for over 45 min after the last injection.[9] The fentanyl infusion dose was calculated from published fentanyl pharmacokinetic data in mechanically ventilated dogs paralyzed with pancuronium.†† 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 carbon dioxide tension as in the conscious animal. Each animal served as its own control for each experiment. Ventilation was maintained with oxygen and nitrogen in concentrations that kept arterial oxygen tension at approximately the same levels as in the conscious animal. Rectal temperature was maintained throughout the experiment by external heating if necessary. Verapamil 200 $\mu g \cdot kg^{-1}$ was injected as in experiment I only after the heart rate and blood pressure had been stable for 20 min in the presence of fentanyl infusion.

During the fentanyl infusion, end-tidal carbon dioxide (Lifespan 100®, Biochem International Inc., Waukesha, WI) concentration was continuously monitored using infrared absorption techniques. Arterial blood gas determinations were made at intervals during anesthesia using a Radiometer ABC® 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 conscious), and they received 3–5 $ml \cdot kg^{-1} \cdot h^{-1}$ lactated Ringer's solution during the experiment.

Effect of Fentanyl Infusion on Cardiac Responses to Verapamil Infusion. Nine conscious dogs received a steady-state infusion of verapamil (200 $\mu g \cdot kg^{-1}$ iv over 3 min, followed by 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 27 min, then another 200 $\mu g \cdot kg^{-1}$ over 3 min, followed by 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 27 min). On another occasion, separated by at least 4 days and in randomly assigned order, these same dogs received an identical verapamil infusion in the presence of fentanyl citrate (500 $\mu g \cdot kg^{-1}$, followed by 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and pancuronium (0.1 $mg \cdot kg^{-1}$). Verapamil infusion was begun after heart rate and blood pressure had been stable for 20 min in the presence of fentanyl infusion. Fluid volumes, ventilation, and monitoring for the dogs receiving fentanyl-pancuronium were the same as described in experiment II. Hemodynamic values and aortic blood samples were collected before and at 27 min during the 3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ steady-state verapamil infusions.

Effect of Fentanyl Infusion and Paralysis with Pancuronium on Cardiac Function. To determine whether the cardiovascular effects of fentanyl infusion were constant in the absence of verapamil in an equivalent period of time to protocol 2, six dogs were given fentanyl citrate (500 $\mu g \cdot kg^{-1}$, followed by 1.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and pancuronium (0.1 $mg \cdot kg^{-1}$). After the heart rate and blood pressure had been stable for 20 min in the presence of fentanyl infusion, the time control study was started. The verapamil infusions in protocol 2 and the time controls in protocol 3 were all begun within 35 min after starting the fentanyl infusions. Fluid volumes, ventilation, and monitoring were maintained as described in experiment II. Hemodynamic values were recorded immediately before, and 30 and 60 min after, starting this time control study.

†† Borel JD, Bentley JE, Gillespie TJ, Gandolfi AJ, Brown BR: Pharmacokinetics of intravenous sufentanil (abstract). ANESTHESIOLOGY 55:A251, 1981

TABLE 1. Effects of Fentanyl Infusion Plus Pancuronium on Verapamil Pharmacokinetics

		Verapamil	Verapamil + Fentanyl
V_1	l	40 ± 4	36 ± 4
Intercompartmental clearance	l/h	211 ± 36	192 ± 44
Vdss	l	101 ± 17	100 ± 14
Total clearance	l/h	54 ± 6	64 ± 9
beta-$t_{1/2}$	hr	1.64 ± 0.27	1.54 ± 0.15

Mean ± SEM.

Sample Analysis

Blood specimens for verapamil were drawn into "venoject" (Becton-Dickinson®, Rutherford, NJ) 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.[10]

Pharmacokinetic Data Analysis

After intravenous verapamil infusion, 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,[11] the pharmacokinetic functions were used to calculate the elimination half-life, total apparent volume of distribution using the steady-state method, and total clearance.[12] 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, and intercompartmental clearance (Q) from the central compartment to the peripheral compartment was determined by the relationship: $Q = K_{12} \times V_1$.[13]

Data Analysis

The effects of verapamil alone and during fentanyl-pancuronium and the effects of fentanyl-pancuronium with time were analyzed using a one-way analysis of variance and BMDP statistical software. Alpha was set at a level of 0.05. When significant ($P < 0.05$ with ANOVA), multiple paired comparisons were applied. However, for each paired comparison, the appropriate level of alpha was determined according to the Bonferroni method.[14] The changes produced by verapamil were assessed by comparing the values recorded at each dose level with: 1) their respective baseline values recorded awake or during fentanyl-pancuronium (*), and 2) the values obtained at the same dose level with verapamil in awake dogs (†). Data are presented as mean ± SEM.

Results

Effects of Fentanyl Infusion on Single-dose Verapamil Pharmacokinetics

Fentanyl infusion plus pancuronium did not affect single-dose verapamil pharmacokinetics (table 1).

Effects of Fentanyl Infusion on Cardiac Responses to Verapamil Infusion

Nine animals were studied. However, not all values were reported for each animal (see "n" in the tables) because of catheter and flow probe failures. Verapamil, at both infusion rates, increased heart rate and PR intervals while decreasing left ventricular dP/dt (fig. 1). The only significant changes induced by fentanyl alone (with pancuronium) were increases in mean arterial pressure and left ventricular dP/dt (table 2).

During fentanyl infusion, left ventricular dP/dt was decreased by both 3 and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ verapamil, while the PR interval was increased in a dose-related manner just as that seen with verapamil in the conscious state (figs. 1, 2). However, unlike in the conscious state, mean arterial pressure was decreased by both doses of verapamil, and heart rate was not changed.

As one would expect from the pharmacokinetic data, plasma levels of verapamil did not differ in the same dogs during fentanyl infusion compared to the conscious state (table 3).

Effect of Fentanyl Infusion on Cardiac Function

This time control study showed no significant change in the hemodynamic effect of fentanyl (plus pancuronium) after 30 and 60 min of infusion compared to control (table 4).

Discussion

Fentanyl infusion plus pancuronium did not affect single-dose verapamil pharmacokinetics or verapamil plasma concentration during steady-state infusion. This is markedly different from the effects seen with either inhalational anesthetics[3] or local anesthetics.[15] Verapamil plasma concentrations and verapamil-induced cardiovascular depression are greater during inhalational anesthesia than in the conscious state.[1,2] It has been shown that the greater cardiovascular depression observed from verapamil infusion during inhalational anesthesia is, at least in part, due to these pharmacokinetic interactions.[16] In fact, when verapamil infusion doses

were adjusted to obtain similar plasma concentrations in the conscious state and during inhalational anesthesia, very little hemodynamic interaction was observed.[16] Thus, the minimal effect of fentanyl, as compared to the inhalational agents, on verapamil hemodynamics when using the same dose of verapamil and the same dog model can be partly explained by the absence of pharmacokinetic interaction.

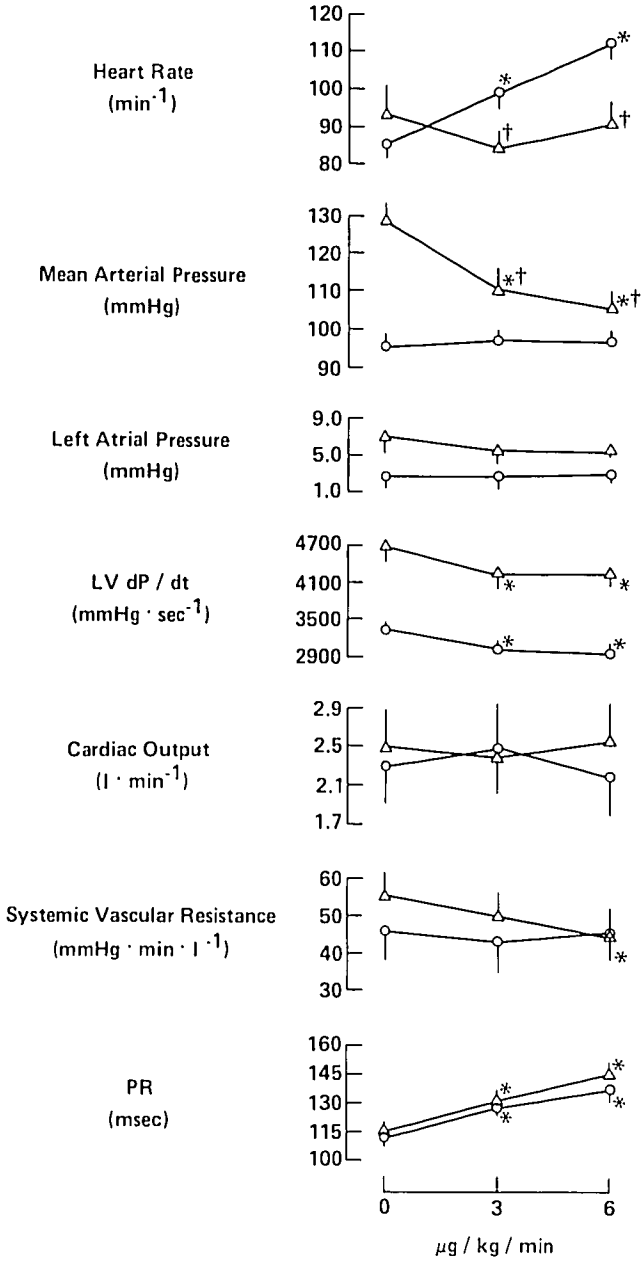

FIG. 1. Effects of verapamil infusions in doses of 0, 3, and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on cardiac function in awake (○) and in fentanyl-anesthetized (△) dogs. *$P < 0.05$ *versus* 0 (respective control values prior to verapamil infusions) †$P < 0.05$ *versus* values recorded at the same dose level during verapamil infusions in awake dogs. For legends see table 2.

TABLE 2. Effects of Fentanyl on Cardiac Hemodynamics and Regional Blood Flow

	(n)	Awake	Fentanyl
HR (min^{-1})	9	82 ± 3	93 ± 8
MAP (mmHg)	9	98 ± 3	128 ± 4*
LAP (mmHg)	6	3.3 ± 1.1	7.0 ± 1.8
CO ($l \cdot min^{-1}$)	5	2.0 ± 0.2	2.5 ± 0.4
LVdP/dt ($mmHg \cdot sec^{-1}$)	8	3410 ± 202	4644 ± 244*
PR (msec)	9	112 ± 5	114 ± 5
CaF ($ml \cdot min^{-1}$)	6	145 ± 19	143 ± 19
CoF ($ml \cdot min^{-1}$)	5	43 ± 12	57 ± 18
ReF ($ml \cdot min^{-1}$)	7	92 ± 10	105 ± 15
SVR ($mmHg \cdot l^{-1} \cdot min^{-1}$)	5	52 ± 4	56 ± 7

Mean ± SEM; HR = heart rate; MAP = mean aortic blood pressure; LAP = mean left atrial blood pressure; CO = cardiac output; LVdP/dt = maximum rate of rise of left ventricular pressure; PR = P-R interval; CaF = carotid blood flow, CoF = coronary blood flow; ReF = renal blood flow; SVR = systemic vascular resistance.
* $P < 0.05$ *vs.* Awake.

The effects of verapamil infusion in the conscious dog were minimal, and were similar to those observed in our previous studies. Fentanyl-pancuronium alone increased mean arterial pressure and left ventricular dP/dt without significantly altering heart rate or left atrial pressure. Fentanyl was not used as an anesthetic *per se* to instrument the animal, but, rather, to study a drug interaction in an unstimulated animal. The dose of fentanyl (1.5 times the ED_{50}) was chosen to compare the effects of verapamil in the presence of fentanyl to the effects of verapamil previously observed in the presence of the inhalational anesthetics using the same dog model.[1,2] The two previous studies, which examined the effects of fentanyl in conscious dogs, reported similar increases in mean arterial pressure, although the doses of fentanyl were smaller.[9,17] Two different groups have reported that fentanyl decreases heart rate in spontane-

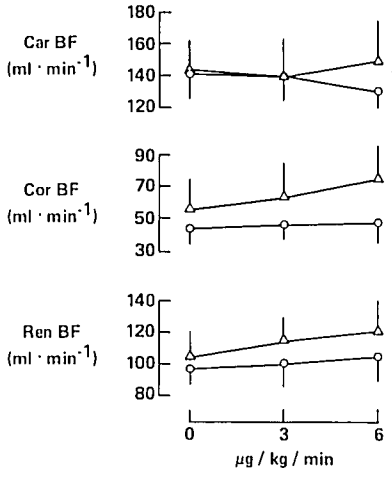

FIG. 2. Effects of verapamil infusions in doses of 0, 3, and 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ on regional blood flow in awake (○) and in fentanyl-anesthetized (△) dogs. For legends see table 2.

TABLE 3. Plasma Verapamil Concentration (ng/ml)

	n	Verapamil Dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	
		3	6
Awake	9	69 ± 6	130 ± 14
Fentanyl	9	76 ± 6	152 ± 11

Mean ± SEM.

ously breathing dogs.[8,9] We noted no significant heart rate changes in our dogs that received fentanyl and pancuronium and whose tracheas were intubated. The vagolytic properties of pancuronium[18] and, possibly, the stimulatory effects of endotracheal intubation blocked the vagotonic action of fentanyl in our study. On the basis of data presented in tables 2 and 4, it is possible to confirm Priano's report that low-dose fentanyl does not significantly affect renal blood flow.[17] In addition, we noted no significant change in coronary or carotid blood flow in the presence of fentanyl-pancuronium. Of particular importance was the demonstration that the hemodynamic effects of fentanyl did not significantly change over 1 h of continuous infusion. This allowed us to interpret the effects of verapamil infusion in the presence of fentanyl-pancuronium as being due to verapamil and not to a change in fentanyl-induced hemodynamics over time.

Fentanyl-pancuronium had minimal effect on the hemodynamic response to verapamil infusion, except for its effect on heart rate and mean arterial pressure changes. In the conscious dogs, verapamil produced a decrease in left ventricular dP/dt, a reflex tachycardia, and no change in mean arterial pressure. Nakaya *et al.* have proposed three explanations for this reflex tachycardia.[19] First, verapamil-induced reductions in myocardial contractility may stimulate ventricular mechanoreceptors that decrease vagal afferent tone and increase sympathetic outflow to the heart. Second, verapamil may directly increase cardiac sympathetic, and decrease cardiac parasympathetic, activity, and, third, verapamil may alter baroreceptor sensitivity. Fentanyl blocked the reflex tachycardia response seen with verapamil in the conscious animal. This is probably due to the central effect fentanyl has of reducing sympathetic tone and increasing vagal tone.[20] Similarly, clinical studies have shown no heart rate change, despite reductions in mean arterial pressure and systemic vascular resistance following bolus verapamil in patients with good left ventricular function during narcotic-based anesthesia.[5,21,22] Verapamil produced similar small reductions in left ventricular dP/dt in the presence and absence of fentanyl-pancuronium, despite the lack of reflex tachycardia in the animals receiving fentanyl-pancuronium.

TABLE 4. Hemodynamic Effects of Fentanyl-pancuronium

	n	Control	30 Min	60 Min
HR (min^{-1})	6	90 ± 5	82 ± 6	80 ± 5
MAP (mmHg)	6	121 ± 7	117 ± 8	116 ± 8
LVdP/dt ($mmHg \cdot sec^{-1}$)	5	3919 ± 520	3799 ± 435	3804 ± 360
ReF ($ml \cdot min^{-1}$)	4	129 ± 13	134 ± 9	130 ± 7
PR (msec)	6	117 ± 6	117 ± 6	113 ± 7

Mean ± SEM. HR = heart rate; MAP = mean aortic blood pressure; LVdP/dt = maximum rate of rise of left ventricular pressure; ReF = renal blood flow; PR = P-R interval.

In contrast to the effects seen with the inhalational anesthetics in this same model, neither fentanyl-pancuronium alone nor verapamil in the presence of fentanyl-pancuronium significantly altered regional blood flows. One animal markedly increased coronary blood flow in response to verapamil in the presence of fentanyl-pancuronium, which increased the average change. However, the other dogs showed little or no change in coronary flow. The maintenance of regional blood flows, despite a decrease in mean arterial pressure, suggests that autoregulation was preserved in the presence of fentanyl-pancuronium.

Fentanyl had no effect on cardiac conduction, which is also different from the inhalational anesthetics. Verapamil increased the PR interval to the same degree in the presence of fentanyl as it did in the conscious animal, and no animals developed A-V block or sinus arrest. This is markedly different from the previously published effects of verapamil during inhalational anesthesia using this same model and same verapamil dosing regimen. Verapamil increased the PR interval to a greater degree during high-dose halothane anesthesia than in the conscious state, and several animals developed A-V block, and even sinus arrest, during inhalational anesthesia.[1,2] However, when verapamil infusion doses were adjusted to obtain similar plasma verapamil concentrations, in the conscious state and during inhalational anesthesia, no effect on cardiac conduction was noted.[16]

In contrast to the inhalational anesthetics, which alter verapamil pharmacokinetics and have mainly additive effects with verapamil on left ventricular contractility, cardiac conduction, and regional blood flows, fentanyl-pancuronium had no effect on verapamil pharmacokinetics, and minimal effect on verapamil pharmacodynamics in healthy dogs.

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