

Cardiovascular Interactions of Lidocaine with Verapamil or Diltiazem in the Dog

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Lidocaine in low and high doses was given by sequential infusions to isoflurane-anesthetized dogs ($1.75 \pm 0.03\%$ end-tidal concentration) with or without concurrent infusions of diltiazem or verapamil, to assess changes in cardiovascular function. When lidocaine was administered alone, the low plasma levels ($\sim 2 \mu\text{g/ml}$) caused only a modest reduction in left ventricular dP/dt. The higher plasma lidocaine levels ($\sim 6 \mu\text{g/ml}$) reduced both left ventricular dP/dt and cardiac index, and increased pulmonary capillary wedge pressure and systemic vascular resistance. Diltiazem or verapamil, when administered alone at plasma concentrations of approximately 150-200 ng/ml, prolonged atrioventricular conduction, decreased heart rate and cardiac index, and, in the case of verapamil, also decreased left ventricular dP/dt and mean arterial pressure. When lidocaine was added to diltiazem or verapamil, the low plasma levels of lidocaine depressed cardiac function in the presence of either calcium channel blocking drug. In the presence of these levels of verapamil or diltiazem, only one of six verapamil-treated animals and three of six diltiazem-treated animals were able to maintain a mean arterial pressure greater than 50 mmHg with the higher dose of lidocaine. Caution may be advised if the addition of lidocaine, by whatever route, is indicated in subjects who have recently received intravenous verapamil or diltiazem. (Key words: Anesthetics, local; lidocaine. Anesthetics, volatile; isoflurane. Heart: myocardial function. Pharmacology: diltiazem; verapamil.)

LIDOCAINE INTERFERES with sodium channel function in myocardial cells.^{1,2} It is frequently administered as a component of an anesthetic: for local or regional nerve blocks,³⁻⁶ to mitigate the autonomic response to laryngoscopy and tracheal intubation,⁷ to suppress the cough reflex,^{8,9} and for antiarrhythmic therapy.^{10,11} In awake subjects, the administration of lidocaine in clinically appropriate doses is usually associated with little, if any, hemodynamic effects.^{12,13} At levels approaching toxicity or in anesthetized subjects, however, lidocaine may be associated with impaired cardiac performance.^{12,14,15} Patients with cardiovascular disease frequently present for anesthesia and surgery while under therapy with a calcium channel blocking drug. Furthermore, they may require therapy with a calcium channel blocking drug intraoperatively. The clinical verapamil preparation is a racemic mixture with both calcium and sodium channel blocking properties, and has been shown at high levels to have local anesthetic properties.¹⁶ Verapamil and li-

docaine have been used in succession and in combination in attempts to treat serious ventricular arrhythmias.¹⁷⁻²⁰ Diltiazem is a calcium channel blocking drug with a similar therapeutic profile to verapamil, and has also been shown to be useful as an antiarrhythmic for calcium channel sensitive arrhythmias.²¹

This study was designed to investigate the effects of adding two levels of lidocaine to plasma levels of verapamil or diltiazem that overlap those thought to be therapeutic in humans, to determine if their combination results in satisfactory cardiovascular function in the presence of anesthetic levels of isoflurane in a canine model.

Materials and Methods

The experimental protocol was approved by the institutional Animal Research Committee. Thirty-nine experiments were performed in 21 conditioned mongrel dogs of either sex with chronic tracheostomies to facilitate an inhalation anesthetic induction.²² The animals weighed $22 \pm 1 \text{ kg}$ (mean \pm SE), and were cared for in accordance with the American Association for Accreditation of Laboratory Animal Care. Anesthesia was induced by isoflurane in 40% oxygen in air through a cuffed tracheostomy tube, and maintained at a level to keep the unparalyzed normocarbic animals immobile and apneic ($1.75 \pm 0.03\%$ end-tidal concentration). Ventilation was controlled. Arterial blood gas tensions and pH were measured with an Instrumentation Laboratories model 813 analyzer (Lexington, MA). Sodium bicarbonate was administered intravenously as needed to correct arterial base deficit. Concentrations of oxygen, carbon dioxide, and isoflurane in the expired gas were measured by mass spectrometry (Perkin Elmer model MGA-1000, Pomona, CA). Temperature was maintained between 38-39° C with a warming blanket and a heat lamp. A peripheral vein was cannulated for fluid and drug administration. Isotonic crystalloid was infused at a rate of $5-7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. A femoral artery was cannulated for obtaining blood samples and for measurement of phasic and mean arterial blood pressure (MAP). A balloon-tipped, flow-directed catheter was positioned in a pulmonary artery *via* an external jugular vein for measurement of right atrial (RA) and pulmonary artery occluded (PAO) pressures, and for determination of thermodilution cardiac outputs in triplicate (Edwards Laboratories cardiac output computer, model 9520, Santa Ana, CA). A micromanome-

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Received from the Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California. Accepted for publication August 18, 1987.

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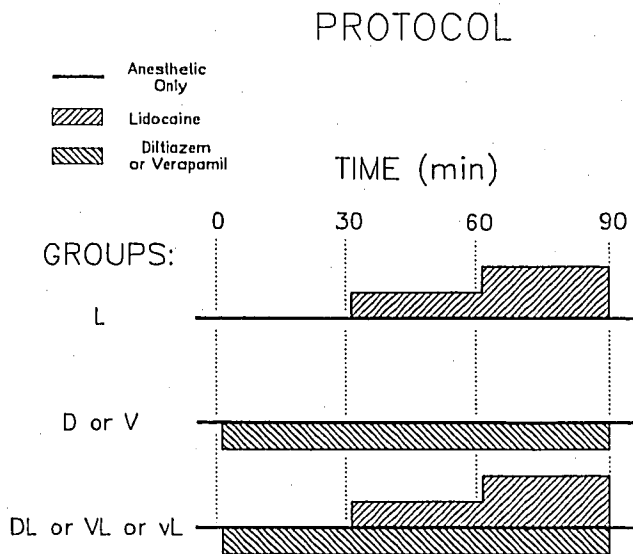


FIG. 1. Experimental protocol. At time 0, all animals were receiving isoflurane ($1.75 \pm 0.03\%$ end-tidal concentration). Group names: L = lidocaine only; D or V = diltiazem or verapamil only; DL or VL or vL = diltiazem, verapamil, or low verapamil plus lidocaine groups. After baseline hemodynamic measurements and plasma samples were taken, groups D, DL, V, and VL received a loading dose ($200 \mu\text{g}/\text{kg}$ over 2 min) followed by a continuous infusion ($10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) of diltiazem or verapamil, respectively. Group vL received a verapamil loading dose of $100 \mu\text{g}/\text{kg}$ over 2 min, followed by a continuous infusion of verapamil at a rate of $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After the 30-min measurements and plasma samples were taken, a loading dose of lidocaine ($1.5 \text{ mg}/\text{kg}$ over 1 min) was given in groups L, DL, VL, and vL, followed by a continuous infusion of lidocaine, $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. After the 60-min measurements and plasma samples, a second lidocaine bolus of $1 \text{ mg}/\text{kg}$ over 1 min was given to groups L, DL, VL, and vL, and the lidocaine infusion rate was increased to $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. Measurements and plasma samples were taken again at 90 min.

ter-tipped catheter (Millar Instruments, Inc, Houston, TX) was positioned in the left ventricle (LV) from a femoral artery for measurement of LV pressure and electronic derivation of LV dP/dt . LV $\text{dP}/\text{dt}_{\text{max}}$ was taken as the peak positive deflection of the dP/dt trace.

Heart rate (HR); femoral arterial, RA, PA, and LV pressures; and LV dP/dt were continuously recorded on a Hewlett Packard® polygraph, model 7758A (Waltham, MA), calibrated daily prior to use. In addition, the electrocardiogram (ECG) was intermittently recorded at fast paper speed ($100 \text{ mm} \cdot \text{s}^{-1}$) for measurement of PR intervals. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated. Arterial plasma verapamil, diltiazem, lidocaine, epinephrine (EPI), and norepinephrine (NEPI) were assayed by high performance liquid chromatography.²³⁻²⁶ Serum levels of electrolytes (Na^+ , K^+ , Cl^-), glucose, and ionized calcium levels were measured using an automated analyzer (Beckman® Instruments, Fullerton, CA). Periodic determinations of serum hematocrit were also made.

After a 1-h stabilization period of being ventilated with isoflurane, baseline cardiovascular measurements and plasma samples were obtained. The baseline ECG was recorded and PR intervals determined. The protocol, consisted of three 30-min periods (fig. 1). Thirty-three of the experiments were initially conducted, divided into five groups. Groups V ($n = 6$) and D ($n = 6$) were given a bolus of verapamil or diltiazem, respectively, followed by a continuous infusion of verapamil or diltiazem for 90 min. Group L ($n = 9$) received only isoflurane for the first 30 min of the protocol, followed at 30 min by a bolus of lidocaine and initiation of a low-dose infusion of lidocaine for the second 30 min. Group L then received an additional bolus and increased lidocaine infusion at 60 min, which continued for the last 30 min of the 90-min protocol. Two combined groups, VL ($n = 6$) and DL ($n = 6$), received verapamil or diltiazem as in groups V and D, and in addition, had the low and high doses of lidocaine added at 30 and 60 min, respectively, as in group L. An additional combined group was then studied ($n = 6$) with a lower infusion rate of verapamil (group vL) to determine if the severe response to the combined administration of verapamil and lidocaine could be altered by reducing the concentration of verapamil.

The bolus and infusion rates used for verapamil and diltiazem in groups V, D, VL, and DL were $200 \mu\text{g}/\text{kg}$ over 2 min, followed by $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The verapamil dose in group vL was $100 \mu\text{g}/\text{kg}$ over 2 min, followed by an infusion of $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The bolus and infusion rates for lidocaine were $1.5 \text{ mg}/\text{kg}$ over 1 min, followed by $100 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the mid 30 min of the protocol, then $1.0 \text{ mg}/\text{kg}$ over 1 min followed by $300 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for the final 30 min of the protocol. Repeat cardiovascular measurements and plasma samples were made at 25 and 30 min of each 30-min study period. An experiment was stopped if mean arterial pressure fell below 50 mmHg. For conservation of animal resources, individual animals were recovered after an experiment. No animal was used more than once in the same drug group, and at least 2 weeks elapsed between experiments in the same animal.

Values are presented in table 1 and figure 1 as the mean \pm standard error of the mean. Statistical analysis for within-group differences over time consisted of analysis of variance for repeated measures with appropriate Bonferroni t tests.²⁷ Analysis of variance was used for intergroup comparisons. If the respective analyses of variance indicated a significant intergroup difference at time zero, appropriate Bonferroni t tests²⁷ were used to look for differences between any of the groups. At other times, when significance was indicated on the intergroup analysis of variance, Bonferroni t tests were used to compare DL, VL, or vL *versus* L; D *versus* DL;

and V or vL *versus* VL. A non-paired *t* test was used to compare the drug levels of verapamil or diltiazem in the V *versus* VL groups and the D *versus* DL groups, and the 90-min lidocaine levels in the L *versus* vL groups. A *P* value of less than 0.05 was considered significant.

Results

Serum electrolytes, glucose, arterial blood gases, temperature, and hematocrit were within normal limits throughout the experiment in all groups. Values for cardiovascular variables and plasma levels of EPI, NEPI, verapamil, diltiazem, and lidocaine for the six study groups are presented in table 1. There were no statistically significant differences among the baseline values for any of the variables measured, except for the baseline EPI value for group V, which was higher than that for group vL. There were no statistically significant differences in the mean 25- and 30-min values in any of the three study periods in any of the six groups for any of the variables measured, indicating a relatively stable condition at the time of measurement. Therefore, the 30-min values are given in the table.

Verapamil and diltiazem plasma levels increased modestly with time when given alone in groups V and D. However, equivalent plasma levels of verapamil or diltiazem were achieved at the respective time periods in groups VL and DL compared to groups V and D. Verapamil levels in group vL were lower than those of group VL, and lidocaine levels were significantly increased at 90 min (high dose) compared to 60 min (low dose) in the groups receiving lidocaine, as intended by the protocol. At 60 min (low dose), the lidocaine level was statistically higher in the VL group compared to the L group (3.1 ± 0.4 *vs.* 1.5 ± 0.1 $\mu\text{g/ml}$).

LIDOCAINE ALONE

In group L, the only change observed with low lidocaine alone was a decrease in LV $\text{dP/dt}_{\text{max}}$ (table 1). At high lidocaine levels, LV $\text{dP/dt}_{\text{max}}$ was further decreased; RA, PAO, and SVR were increased; and CI decreased. EPI levels were decreased with both levels of lidocaine.

DILTIAZEM AND DILTIAZEM-LIDOCAINE

In group D, diltiazem caused a decrease in HR and CI, and a prolongation of the PR interval. With the addition of low levels of lidocaine (group DL), RA and PAO were increased; LV $\text{dP/dt}_{\text{max}}$ and CI were decreased; and PR interval continued prolonged. With the high lidocaine levels, three animals were unable to maintain a MAP greater than 50 mmHg. When MAP

decreased below 50 mmHg, the study was abandoned in those three animals and the drug infusions stopped. The intravenous administration of calcium chloride, 500 mg, one or two doses, promptly increased blood pressure and cardiac output.

VERAPAMIL AND VERAPAMIL-LIDOCAINE

In group V, verapamil caused a decrease in HR, MAP, LV $\text{dP/dt}_{\text{max}}$, and CI, with a prolongation of the PR interval. Upon adding low levels of lidocaine in group VL, MAP, CI, and LV $\text{dP/dt}_{\text{max}}$ declined to quite low levels; RA, PAO, SVR, EPI, and NEPI were increased, and PR interval again was prolonged. In one animal, MAP decreased to 50 mmHg, and the study was aborted as above. Only one of the five animals remaining in the study could maintain a blood pressure greater than 50 mmHg when the lidocaine infusion rate was increased.

In group vL, the lower levels of verapamil prolonged the PR interval. The only change caused by the addition of low levels of lidocaine was a decrease in LV $\text{dP/dt}_{\text{max}}$. The high level of lidocaine was tolerated by all animals at the lower levels of verapamil, although, with decreased HR, MAP, CI, and LV $\text{dP/dt}_{\text{max}}$, and increased RA, PAO, SVR, and EPI levels.

As stated previously, as the lidocaine levels increased, 3/6 diltiazem treated dogs and 5/6 verapamil treated dogs were unable to complete the experimental protocol because of severe hypotension (MAP < 50 mmHg). In those latter animals, SVR and PAO were increased, and CI and LV $\text{dP/dt}_{\text{max}}$ were severely decreased. Conduction block occurred in four of the five VL animals that ultimately became hypotensive. Wenckebach 2° heart block occurred in two animals, 2° heart block with 2:1 conduction occurred in one animal, and a junctional rhythm occurred in the fourth animal. HR decreased from 105–125 to 50–80 beats per minute, with the development of conduction block. Treatment of the depressed blood pressure with calcium chloride, as described previously, restored sinus rhythm in the three animals with 2° heart block (transiently in one case), but did not affect the junctional rhythm in the fourth animal.

Plasma samples were taken for drug levels at the time the three DL animals and the five VL animals had to be withdrawn from the study because of hypotension. In the face of hemodynamic compromise in those three DL animals, plasma diltiazem levels had risen to 348 ± 28 ng/ml and lidocaine levels had risen to 16.4 ± 5.9 $\mu\text{g/ml}$. At the time the study was aborted in the five VL animals because of hypotension, the verapamil levels were 187 ± 33 ng/ml and the lidocaine levels were 5.3 ± 1.7 $\mu\text{g/ml}$.

TABLE 1. Cardiovascular Values and Plasma Levels of NEPI, EPI, Lidocaine, Diltiazem, and Verapamil for Groups L (Lidocaine Only); D (Diltiazem Alone); DL (Diltiazem + Lidocaine); V (Verapamil Only); VL (Verapamil + Lidocaine); and vL (Low Verapamil + Lidocaine)

	Time (Min)	Group					
		L	D	DL*	V	VL*	vL
n		9	6	6	6	6	6
HR (bpm)	B	125 ± 4	143 ± 3	137 ± 5	142 ± 10	137 ± 3	132 ± 5
	30	133 ± 4†	D 129 ± 4†	D 124 ± 4†	V 124 ± 4†	V 122 ± 4†	v 126 ± 2
	60	130 ± 4	D 127 ± 3†	DL 120 ± 4†‡	V 119 ± 3†	VL 86 ± 13†§	vl 118 ± 3
	90	L 124 ± 5	D 127 ± 3†	DL 115 ± 1 (n = 3)	V 116 ± 2†	VL	vL 105 ± 4†§
MAP (mmHg)	B	95 ± 7	80 ± 3	80 ± 5	86 ± 7	90 ± 8	90 ± 7
	30	92 ± 6	D 75 ± 4	D 75 ± 4	V 74 ± 5†	V 72 ± 7†	v 78 ± 5
	60	85 ± 5	D 77 ± 2	DL 78 ± 4	V 73 ± 6†	VL 55 ± 3†§	vl 84 ± 6¶
	90	L 80 ± 5	D 80 ± 3	DL 73 ± 2 (n = 3)	V 79 ± 3	VL	vL 70 ± 8†
RA (mmHg)	B	4 ± 1	4 ± 1	5 ± 1	6 ± 1	5 ± 1	5 ± 1
	30	4 ± 1	D 4 ± 1	D 5 ± 1	V 7 ± 1	V 7 ± 1§	v 6 ± 1
	60	5 ± 1	D 3 ± 1¶	DL 7 ± 1†‡	V 7 ± 1	VL 9 ± 1†	vl 6 ± 1
	90	L 7 ± 1†	D 4 ± 1	DL 9 ± 2 (n = 3)	V 7 ± 1	VL	vL 10 ± 1†‡
PAO (mmHg)	B	7 ± 1	7 ± 1	8 ± 1	7 ± 1	7 ± 1	8 ± 1
	30	7 ± 1	D 8 ± 1	D 7 ± 1	V 9 ± 1	V 9 ± 1	v 8 ± 1
	60	8 ± 1	D 6 ± 1	DL 9 ± 1†‡	V 9 ± 2	VL 13 ± 1†‡	vl 10 ± 1
	90	L 11 ± 1†‡	D 7 ± 1	DL 13 ± 2 (n = 3)	V 9 ± 1	VL	vL 12 ± 1†‡
LV dp/dt (mmHg/s)	B	2183 ± 330	2375 ± 139	2300 ± 184	3026 ± 596	2302 ± 109	2650 ± 280
	30	2472 ± 349	D 2117 ± 117	D 2017 ± 221	V 2258 ± 301†	V 1790 ± 308	v 2258 ± 258
	60	1867 ± 208‡	D 2083 ± 133	DL 1592 ± 80†‡	V 1875 ± 265†	VL 1225 ± 203†‡	vl 1846 ± 301†
	90	L 1272 ± 159†‡	D 1983 ± 128	DL 1067 ± 88 (n = 3)	V 1667 ± 194†	VL	vL 1075 ± 191†
CI (l · min ⁻¹ · m ⁻²)	B	5.2 ± 0.4	6.5 ± 0.8	4.9 ± 0.4	7.0 ± 0.8	5.2 ± 0.5	7.0 ± 0.7
	30	5.4 ± 0.4	D 5.7 ± 0.9	D 4.3 ± 0.5	V 6.0 ± 0.6	V 4.0 ± 0.6†	v 6.8 ± 0.5¶
	60	4.7 ± 0.4	D 5.0 ± 0.7†	DL 3.6 ± 0.5†	V 5.1 ± 0.4†¶	VL 2.1 ± 0.5†‡§	vl 5.4 ± 0.7¶
	90	L 3.0 ± 0.4†	D 4.7 ± 0.8†	DL 2.8 ± 0.6 (n = 3)	V 4.2 ± 0.5†	VL	vL 2.7 ± 0.6†‡
SVR (dynes · s · cm ⁻⁵)	B	1656 ± 176	1128 ± 89	1454 ± 236	1116 ± 176	1567 ± 172	1183 ± 163
	30	1569 ± 149	D 1208 ± 99	D 1574 ± 273	V 1032 ± 97¶	V 1611 ± 166	v 977 ± 77§¶
	60	1675 ± 210	D 1470 ± 121	DL 2004 ± 423	V 1154 ± 82¶	VL 2633 ± 679†‡	vl 1385 ± 123¶
	90	L 2529 ± 354†‡	D 1684 ± 197	DL 2262 ± 468 (n = 3)	V 1640 ± 231†	VL	vL 2280 ± 340†‡
PR (ms)	B	114 ± 4	119 ± 7	122 ± 3	110 ± 3	123 ± 8	114 ± 7
	30	113 ± 4	D 148 ± 10†	D 142 ± 6†§	V 152 ± 9†	V 171 ± 19†§	v 138 ± 8†
	60	113 ± 3	D 156 ± 7†	DL 147 ± 7†§	V 163 ± 12†	VL 189 ± 23†§	vl 147 ± 8†§
	90	L 114 ± 3	D 165 ± 12†	DL 150 ± 12 (n = 3)	V 169 ± 14†	VL	vL 166 ± 16†§
NEPI (pg/ml)	B	137 ± 20	91 ± 32	126 ± 19	154 ± 45	161 ± 29	82 ± 19
	30	132 ± 28	D 125 ± 32	D 119 ± 28	V 227 ± 57	V 238 ± 45	v 148 ± 32
	60	98 ± 16	D 130 ± 39	DL 157 ± 27	V 202 ± 49	VL 481 ± 179†¶	vl 155 ± 36
	90	L 97 ± 10	D 124 ± 31	DL 109 ± 7 (n = 3)	V 211 ± 48	VL	vL 362 ± 124
EPI (pg/ml)	B	577 ± 95	313 ± 38	693 ± 131	800 ± 224	475 ± 145	291 ± 31
	30	428 ± 80	D 337 ± 70	D 473 ± 132	V 659 ± 144	V 474 ± 146	v 439 ± 86
	60	335 ± 95†	D 291 ± 69	DL 534 ± 214	V 626 ± 119	VL 2017 ± 918†‡§	vl 421 ± 160
	90	L 315 ± 105†	D 202 ± 56	DL 201 ± 129 (n = 3)	V 478 ± 93	VL	vL 1232 ± 490†
V or D (ng/ml)	B	—	—	—	—	—	—
	30	—	D 117 ± 9	D 129 ± 20	V 140 ± 19	V 124 ± 9	v 73 ± 9¶
	60	—	D 160 ± 8‡	DL 163 ± 10	V 184 ± 27	VL 164 ± 30‡	vl 57 ± 4¶
	90	—	D 193 ± 17‡	DL 196 ± 41 (n = 3)	V 226 ± 40	VL	vL 84 ± 10†
L (ug/ml)	B	—	—	—	—	—	—
	30	—	—	—	—	—	—
	60	1.5 ± 0.1	—	DL 2.4 ± 0.7	—	VL 3.1 ± 0.4§	vl 2.5 ± 0.4
	90	L 5.8 ± 0.6‡	—	DL 6.3 ± 1.7 (n = 3)	—	VL	vL 7.8 ± 1.0‡

Mean ± SEM. For clarity, the drugs present at the different time periods for the six experimental groups are shown next to the values: l = low lidocaine; L = high lidocaine; D = diltiazem; V = verapamil; v = low verapamil.

* DL group: 90 min, n = 3 animals remaining in study (i.e., MAP > 50 mmHg). VL group: 60 min, n = 5 animals remaining in study (i.e., MAP > 50 mmHg), comparisons for significance of 60-min values in VL group made only to previous values for those five dogs; 90 min,

no value shown because only one animal remaining in study with MAP > 50 mmHg.

Within group comparisons: †P < 0.05 compared to baseline value for that group; ‡P < 0.05 compared to preceding value for that group.

Inter-group comparisons: At baseline (B), there were no significant differences among groups, except for EPI, vL < V. §P < 0.05 comparing DL, VL, or vL to L; ¶P < 0.05 comparing D to DL; V or vL to VL.

Discussion

Other work from this same laboratory has demonstrated that similar canine models anesthetized with approximately the same concentration of isoflurane are hemodynamically stable over the time period encompassed by this experiment.²⁸ The verapamil and diltiazem levels achieved in groups V, VL, D, and DL are in the therapeutic range for humans, which is approximately 50–200 ng/ml for both drugs,^{29–31} and also within the range that produces typical pharmacodynamic effects of calcium channel blockade upon intracardiac conduction in anesthetized dogs.^{32–34} The lidocaine levels achieved with the low dose of lidocaine are at the lower end of the therapeutic antiarrhythmic range (1.5–6 µg/ml) in man,¹⁰ and equivalent to plasma levels achieved during local and regional anesthesia^{3–6} or from doses of lidocaine sufficient to suppress cardiovascular responses to tracheal intubation.⁷ Plasma lidocaine levels of approximately 3.5 µg/ml were sufficient to suppress ischemic induced arrhythmias in the dog.³⁵ The high lidocaine levels are at or just above the upper advisable therapeutic antiarrhythmic level in man.¹⁰ Similar levels have been reached in man during bolus administration of lidocaine for cough suppression during tracheal intubation.⁹

When given alone, the verapamil and diltiazem in groups V and D caused the anticipated interference with intracardiac conduction, as well as the usual hemodynamic profile seen with these plasma drug levels in isoflurane anesthetized dogs.^{28,32,33} At baseline, group V had numerically greater values for mean EPI level and LV dp/dt_{max} than the other groups. The baseline mean EPI value for group V did prove statistically different from that of group vL. However, the mean LV dp/dt_{max} value, with large variability, did not reach a level of statistical significance compared to the other groups using analysis of variance. Other mean baseline variables for group V (including HR, MAP, PAO, CI, and SVR) were numerically and statistically equivalent to other groups. Thus, no effects of the group V baseline EPI level and LV dp/dt_{max} values could be detected in the more commonly measured variables in group V at baseline.

In the present study, the diltiazem-treated dogs tolerated the addition of equivalent levels of lidocaine more favorably than did the verapamil-treated dogs at similar calcium channel blocking drug plasma levels. In a previous study, in the presence of halothane anesthesia, diltiazem-treated dogs tolerated the addition of propranolol more favorably than verapamil-treated dogs at approximately equal plasma levels of verapamil and diltiazem.³⁴ The same untoward effects as those seen with

verapamil may ultimately occur if lidocaine or propranolol were added to higher levels of diltiazem, as the effects of all of these drugs can be expected to be plasma level related.^{28,32,33,36,37} As evidence in the opposite direction, the vL group tolerated the lidocaine much better than the VL group. Results such as these would suggest that, at therapeutic levels of diltiazem, as compared to verapamil, there may be more of a safety margin if other cardiovascularly depressant drugs are indicated in combination.

The question remains whether the combined effects of lidocaine and the calcium channel blocking drugs tested in this study result from a pharmacokinetic effect or from a combined effect on calcium homeostasis. Preliminary data from Dlewati *et al.*³⁸ indicated that, at normal levels of cardiovascular function, adding lidocaine to a continuous infusion of verapamil in conscious dogs caused a decrease in verapamil plasma level because of an alteration in the distribution of verapamil. Lidocaine pharmacokinetics were reported to be unchanged by verapamil under their conditions. The significant difference in low lidocaine levels between the VL and L groups in the present study may have been a result of the concomitant presence of verapamil; however, the possibility that this difference represents the inherent variability of the drug administration technique among different groups of animals cannot be excluded.

With regard to the higher infusion rates of lidocaine used in the last period of the present study, there is evidence that hepatically metabolized drugs, such as lidocaine, verapamil, or diltiazem, can be expected to accumulate in the presence of hepatic dysfunction or hepatic underperfusion.^{39–42} While we did not measure pharmacokinetic parameters in this study, it is likely that impairment of cardiac function led to a decreased clearance of the drugs in those DL animals with hypotension that had to be eliminated from the study. Increased plasma levels would then lead to worsening cardiac function in an ever-depressant spiral. In the VL group, however, the mean plasma levels for the five animals with severe hypotension were not different from those in the V group at the comparable time. The severe depression in a number of animals in the DL and VL groups at the higher levels of lidocaine may relate to evidence that sodium channel blockade itself can lead to impairment of intracellular calcium homeostasis, perhaps by adversely affecting normal sodium-calcium exchange mechanisms,⁴³ thus resulting in further depression of myocardial and vascular contractility. Sodium channel blocking drugs, such as lidocaine, may also contribute to depressed myocardial contractility by altering calcium release from the sarcoplasmic reticulum.⁴⁴

The reduction of the EPI levels which occurred when lidocaine was added to isoflurane anesthesia may have occurred because of the effect of lidocaine to deepen the anesthetic level.⁴⁵ EPI and NEPI levels were, nevertheless, elevated in the verapamil-treated dogs when hemodynamic compromise occurred in the presence of lidocaine. The elevations in circulating catecholamine levels may have served to mitigate otherwise worse additive effects of lidocaine and verapamil. The results observed, however, are consistent with other studies which demonstrate that, ultimately, autonomic compensatory efforts by the subject may prove insufficient to overcome the depressant effects of verapamil or diltiazem in the presence of inhalation anesthetics.^{34,46}

The clinical implication of this study is that caution may be advised if the addition of lidocaine by whatever route is indicated in patients who have recently received intravenous verapamil or diltiazem in the setting of isoflurane anesthesia. In the presence of acutely administered verapamil or diltiazem, care should be taken to avoid high peak plasma levels of lidocaine that would contribute to a depressed cardiovascular system and reduced vital organ perfusion. The influence of other anesthetics or anesthetic adjuvants is unknown, as are the effects of administering lidocaine to subjects receiving chronic oral diltiazem or verapamil therapy.

The authors thank Thomas Patin and Owen Buchea for technical assistance, and Tony Law and Mercedes Espiritu for performing the plasma assays.

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