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The Cardiovascular and Adrenergic Actions of Verapamil or Diltiazem in Combination with Propranolol during Halothane Anesthesia in the Dog

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Continuous infusions of verapamil and diltiazem were established in halothane-anesthetized dogs (1.15–1.35% end tidal concentration) with or without a concomitant propranolol infusion to investigate changes: in cardiovascular function, in reflex activation as reflected in circulating catecholamine levels, and in the chronotropic response to the exogenously administered beta agonist, isoproterenol. Verapamil plasma levels of approximately 100 and 250 ng · ml^{-1}, diltiazem plasma levels of approximately 140 and 325 ng · ml^{-1}, and propranolol levels of approximately 70 ng · ml^{-1} were tolerated individually in the presence of halothane, although atrioventricular conduction was prolonged in the verapamil and diltiazem groups. Catecholamine levels were increased in the high verapamil group. However, when propranolol was combined with the lower levels of verapamil or diltiazem, the result was decreased heart rate, blood pressure, left ventricular maximum rate of tension development (dP/dt), and cardiac index with increased systemic vascular resistance. When the attempt was made to proceed to the increased plasma levels of verapamil or diltiazem in the presence of propranolol, 6/6 animals in the verapamil-propranolol group and 4/6 animals in the diltiazem-propranolol group were unable to maintain a mean arterial blood pressure of greater than 50 mmHg, and many developed 2° or higher heart block. Analysis of the plots of the logarithms of the doses of isoproterenol *versus* changes in heart rate revealed that larger amounts of isoproterenol were required to achieve the same increase in heart rate as with halothane alone if these plasma levels of propranolol, verapamil, or diltiazem individually were present, and that very much larger doses of isoproterenol were required to increase heart rate to the same level as with halothane alone when a combined block with verapamil or diltiazem plus propranolol was present. (Key words: Anesthetics, volatile: halothane. Heart: myocardial function. Pharmacology: diltiazem; verapamil. Sympathetic nervous system, beta-adrenergic blockade: propranolol.)

THE EFFECTS OF CALCIUM channel blocking drugs may be altered by the concomitant administration of beta-adrenergic blocking drugs in two ways: a) compensatory reflex responses to the direct depressant effects of calcium channel blocking drugs may be diminished, and b) beta-adrenergic blockade, by lowering intracellular levels of cyclic AMP, reduces the number of calcium channels available for calcium influx,[1] which will leave even fewer channels functional after the subsequent administration of a calcium channel blocking drug.

Diltiazem or verapamil may be combined with beta blockers for the treatment of angina pectoris.[2,3] In addition, the suitability of either verapamil/diltiazem[4,5] or propranolol[6] to slow nodal conduction for the treatment of supraventricular arrhythmias is another area in which combined therapy may be considered. The hemodynamic and conduction effects of verapamil have been shown to be potentiated by beta blockade.[7,8] Intravenous co-administration would appear to be particularly hazardous.[8–10] Potentiation of the effects of diltiazem by beta blockade has not been thoroughly investigated.[11]

In the perioperative period, situations are frequently encountered when patients develop supraventricular tachydysrhythmias in the presence of inhalation anesthetics. Halothane has been shown not only to have combined depressant effects with verapamil,[12,13] but also to interfere with reflex compensatory mechanisms.[14,15] This study was designed to compare the effects of adding propranolol to two plasma levels of verapamil or diltiazem in a halothane-anesthetized animal model. To address adrenergic interactions, changes were measured in cardiovascular function, in reflex activation as reflected in circulating catecholamine levels, and in the chronotropic response to an exogenously administered beta agonist.

Methods

Thirty-four experiments were carried out in 17 conditioned mongrel dogs of either sex weighing 21 ± 3 kg (mean ± SE), cared for in accordance with the American Association for Accreditation of Laboratory Animal Care. Anesthesia was induced by halothane in 40% oxygen in air and maintained through a cuffed endotracheal tube at a level sufficient to keep the unparalyzed normocarbic animals immobile and apneic (1.15–1.35% end tidal concentration). Ventilation was controlled. Arterial blood gas tensions and *p*H were measured with an Instrumentation Laboratories model 813 analyzer. Sodium bicarbonate was administered intravenously as needed to correct arterial base deficits. The range of bicarbonate administered

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was between 50–150 mEq over the course of the experiment and was related to the protocol requirement for repeated isoproterenol testing. In a previous study with epinephrine challenges it was observed that including bicarbonate in the intravenous infusion mitigated acute changes in base deficit related to this type of transient physiologic stress.[16]

Concentrations of oxygen, carbon dioxide, and halothane in the expired gas were measured by mass spectrometry (Perkin Elmer model MGA-1000). 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 $ml \cdot kg^{-1} \cdot h^{-1}$. 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 Laboratory cardiac output computer, model 9520). A micromanometer-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.

Heart rate (HR); femoral arterial, RA, PA, and LV pressures; and LV dP/dt were continuously recorded on a Hewlett Packard® polygraph, model 7758A, calibrated daily prior to use. In addition, the electrocardiogram (ECG) was intermittently recorded at fast paper speed ($100\ mm \cdot s^{-1}$) for measurement of PR intervals. Cardiac index (CI) and systemic vascular resistance (SVR) were calculated. Arterial plasma verapamil, diltiazem, propranolol, epinephrine (EPI), and norepinephrine (NEPI) were assayed by high-performance liquid chromatography.[17–19] Serum levels of electrolytes (Na^+, K^+, Cl^-), glucose, and ionized calcium levels were measured using an automated analyzer (Beckman Instruments, Irvine, CA). Periodic determinations of serum hematocrit were also made.

After a 1-h stabilization period of being ventilated with halothane, control cardiovascular measurements and plasma samples were obtained. The baseline ECG was recorded and PR intervals determined. The chronotropic response to graded doses of isoproterenol was then determined by administering three of the following isoproterenol doses (0.02, 0.05, 0.15, 0.50, 1.00, and 2.00 $\mu g \cdot kg^{-1}$) at 10 min intervals and determining the maximum change in heart rate. During this evaluation, a plot of the log of the isoproterenol dose *versus* change in heart rate was constructed, and, for each curve, doses of isoproterenol were chosen to produce heart rate changes in the straight central portion of the dose response curve.

PROTOCOL

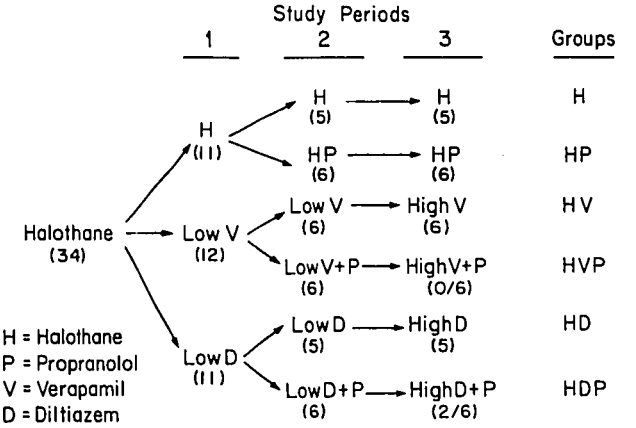

FIG. 1. Drug administration protocol. During the control period, end-tidal concentrations of halothane were 1.1–1.3%. In study period 1 (see text): 11/34 subjects continued to receive halothane (groups H + HP); in 12 experiments, verapamil (V) was added (groups HV + HVP); in 11 experiments, diltiazem (D) was added (groups HD and HDP). In study period 2: one-half of each of these groups had propranolol (P) infusions added along with continuation of the low infusion rate of V or D (groups HP, HVP, HDP). In study period 3, the V or D infusion rates were increased in groups HV, HVP, HD, and HDP.

Cardiovascular measurements and plasma samples were then repeated 20 min after the last isoproterenol dose for comparison with the pre-isoproterenol values.

The experiments were then divided into six groups of five or six animals each: group H = halothane alone (n = 5); group HP = halothane + propranolol (n = 6); group HV = halothane + verapamil (n = 6); group HVP = halothane + verapamil + propranolol (n = 6); group HD = halothane + diltiazem (n = 5); and group HDP = halothane + diltiazem + propranolol (n = 6). There were then three drug study periods of the experiment, each of which consisted of initiation of a drug infusion; measurements and plasma samples at 30 and 35 min of infusion; continuation of the infusion with an isoproterenol dose-response test performed as described; and repeat measurements 20 min after the last isoproterenol test, which served as control measurements for the next study period. The drug administration protocol is shown in figure 1. In the first study period, groups H and HP continued to receive only halothane; groups HV and HVP received verapamil, 150 $\mu g \cdot kg^{-1}$ over 2 min followed by a verapamil infusion of 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; and groups HD and HDP received a bolus of diltiazem of 200 $\mu g \cdot kg^{-1}$ over 2 min followed by an infusion of diltiazem of 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the second study period, group H continued to receive only halothane; groups HV and HD continued to receive the verapamil and diltiazem infusions as described; while, in groups HP, HVP, and HDP, propranolol was added with a bolus of 150 $\mu g \cdot kg^{-1}$ followed

TABLE 1. Cardiovascular, Arterial Serum Chemistry, and Catecholamine Values for Group H (Halothane Only) at Control and at 30 Min of Each of the Three Study Periods

	Control	Period 1	Period 2	Period 3
n	5	5	5	5
HR (bpm)	125 ± 4	129 ± 3	127 ± 3	120 ± 8
MAP (mmHg)	97 ± 3	98 ± 7	99 ± 5	98 ± 3
RA (mmHg)	4 ± 1	5 ± 2	5 ± 2	5 ± 2
PAO (mmHg)	7 ± 1	8 ± 1	8 ± 1	8 ± 1
LV dP/dt ($mmHg \cdot s^{-1}$)	1950 ± 137	2060 ± 122	1930 ± 111	1910 ± 151
CI ($l \cdot min^{-1} \cdot m^{-2}$)	6.08 ± 0.74	5.84 ± 0.58	5.49 ± 0.87	4.78 ± 0.49
SVR ($dynes \cdot s \cdot cm^{-5}$)	1561 ± 187	1645 ± 301	1867 ± 387	1993 ± 297
PR Interval (ms)	128 ± 8	121 ± 14	125 ± 9	124 ± 5
Arterial pH	7.35 ± 0.01	7.35 ± 0.01	7.37 ± 0.02	7.36 ± 0.02
PaO_2 (mmHg)	182 ± 11	166 ± 7	175 ± 11	175 ± 14
$PaCO_2$ (mmHg)	35 ± 2	37 ± 1	34 ± 1	34 ± 1
$[Na^+]$ ($mEq \cdot l^{-1}$)	148 ± 1	—	147 ± 1	144 ± 2
$[K^+]$ ($mEq \cdot l^{-1}$)	3.6 ± 0.1	—	3.3 ± 0.3	3.7 ± 0.1
$[Cl^-]$ ($mEq \cdot l^{-1}$)	108 ± 2	—	106 ± 2	108 ± 2
$[Ca^{++}]$ ($mM \cdot l^{-1}$)	2.00 ± 0.08	—	1.92 ± 0.08	1.94 ± 0.08
Glucose (mg%)	115 ± 4	—	109 ± 6	115 ± 6
Temperature (°C)	38.2 ± 0.4	38.6 ± 0.2	38.7 ± 0.3	39.0 ± 0.2
NEPI ($pg \cdot ml^{-1}$)	105 ± 27	94 ± 27	103 ± 25	145 ± 36
EPI ($pg \cdot ml^{-1}$)	568 ± 236	403 ± 175	247 ± 70	302 ± 131

Mean ± SEM

by an infusion of 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In the third and final study period, a second bolus of calcium channel blocker was given and the infusion rate increased: in groups HV and HVP to 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of verapamil, and in groups HD and HDV to 12 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of diltiazem. The experiment was stopped if mean arterial pressure fell below 50 mmHg. At least 2 weeks elapsed between experiments with the same animal. No animal was used more than once in the same drug group.

To compare dogs receiving different isoproterenol dose combinations, the best fit linear equation for the double reciprocal plot of the inverse of the isoproterenol dose *versus* the inverse of the heart rate change was determined for each isoproterenol dose-response test in each animal. These equations were then solved for the range of isoproterenol doses. Mean heart rate changes for each isoproterenol dose could then be calculated for an entire group, which were then plotted in the more familiar form as a function of the logarithm of the isoproterenol dose. The equations were also solved for the dose of isoproterenol required to increase the heart rate by 40 beats per min, the chronotropic dose 40 (CD_{40}). The mean CD_{40} was calculated for each group for each experimental period.

Values are presented in the tables and figures as the mean ± standard error of the mean. Data analysis consisted of analysis of variance and analysis of variance for repeated measures with Bonferroni-corrected *t* tests, and nonpaired *t* tests. Analysis of variance tests with Bonferroni-corrected *t* tests were also utilized for the log-transformed CD_{40} values in order to evaluate the effects of time on the heart rate response to isoproterenol for the halothane group, and to make comparisons among the different groups. A *P* value 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 the groups. There were no differences compared to group H in any of the variables measured at the time of the initial measurements. There was no statistically significant differences in the mean 30 and 35 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 figures and tables. There also were no significant differences between any of the mean pre- and 20 min post-isoproterenol values.

In group H (halothane only), there were no significant changes with time in cardiovascular, arterial serum chemistry, or catecholamine values over the duration of the three study periods (Table 1). Similarly, there were no changes in group HP over the course of period 1, nor were there any differences between groups H and HP during period 1, when both groups were receiving only halothane. There were no significant differences between groups HV and HVP, or between HD and HDP, in period 1 when only calcium channel blocker was present. In addition, there were no significant changes in measured values for groups HV or HD comparing period 1 to period 2.

TABLE 2. Cardiovascular and Arterial Serum Chemistry Values and Plasma Levels of NEPI, EPI, Propranolol, Verapamil, and Diltiazem for Period 2 for Groups H (Halothane Only); HP (Halothane + Propranolol); HV (Halothane + Low Verapamil); HVP (Halothane + Low Verapamil + Propranolol); HD (Halothane + Low Diltiazem); and HDP (Halothane + Low Diltiazem + Propranolol)

	Period 2					
	H	HP	HV	HVP	HD	HDP
n	5	6	6	6	5	6
HR (bpm)	127 ± 3	116 ± 6	117 ± 5	99 ± 8*†	120 ± 3	92 ± 4*†
MAP (mmHg)	99 ± 5	105 ± 6	85 ± 6	68 ± 8*†	101 ± 5	82 ± 4
RA (mmHg)	5 ± 2	3 ± 1	8 ± 2	9 ± 1*	8 ± 1	8 ± 1
PAO (mmHg)	8 ± 1	7 ± 1	10 ± 1	13 ± 1*†	9 ± 1	10 ± 1
LV dP/dt (mmHg · s^{-1})	1930 ± 111	1558 ± 134	1383 ± 135	775 ± 125*†	1567 ± 99	1117 ± 83*†
CI (l · min^{-1} · m^{-2})	5.49 ± 0.87	4.37 ± 0.55*	4.33 ± 0.56	1.69 ± 0.34*†	4.66 ± 0.82	2.82 ± 0.50*†
SVR (dynes · s · cm^{-5})	1867 ± 387	2466 ± 384*	1984 ± 355	3415 ± 274*†	1963 ± 250	2598 ± 367*†
PR Interval (ms)	125 ± 9	143 ± 8	161 ± 10*	200 ± 21*†	168 ± 13*	164 ± 12*
Arterial pH	7.36 ± 0.01	7.35 ± 0.02	7.37 ± 0.01	7.37 ± 0.02	7.37 ± 0.02	7.39 ± 0.01
PaO_2 (mmHg)	166 ± 8	172 ± 12	198 ± 8	149 ± 20	165 ± 5	169 ± 20
$PaCO_2$ (mmHg)	36 ± 2	35 ± 2	34 ± 1	37 ± 2	33 ± 2	32 ± 2
$[Na^+]$ (mEq · l^{-1})	147 ± 1	147 ± 2	144 ± 2	139 ± 8	150 ± 4	147 ± 1
$[K^+]$ (mEq · l^{-1})	3.3 ± 0.3	3.6 ± 0.2	3.5 ± 0.1	3.6 ± 0.2	3.9 ± 0.2	3.7 ± 0.1
$[Cl^-]$ (mEq · l^{-1})	106 ± 2	107 ± 1	111 ± 1	107 ± 5	117 ± 4	113 ± 1
$[Ca^{++}]$ (mM · l^{-1})	1.92 ± 0.08	1.95 ± 0.06	1.82 ± 0.05	1.91 ± 0.11	1.95 ± 0.01	1.72 ± 0.9
Glucose (mg%)	109 ± 6	104 ± 4	109 ± 7	101 ± 11	105 ± 8	101 ± 7
Temperature (°C)	38.7 ± 0.3	39.0 ± 0.1	38.2 ± 0.2	39.3 ± 0.2	38.7 ± 0.1	38.2 ± 0.4
NEPI (pg · ml^{-1})	103 ± 25	91 ± 20	286 ± 70	771 ± 221*†	190 ± 21	175 ± 74
EPI (pg · ml^{-1})	247 ± 69	381 ± 102	1048 ± 307	4539 ± 1163*†	183 ± 41	641 ± 220
V (ng · ml^{-1})			134 ± 18	163 ± 16		
D (ng · ml^{-1})					175 ± 12	213 ± 24
P (ng · ml^{-1})		62 ± 10		73 ± 6		76 ± 14

Mean ± SEM.
* = $P < 0.05$ compared to no calcium channel blocker.
† = $P < 0.05$ compared to equivalent group without propranolol.

Hemodynamic values; PR interval of the ECG; plasma propranolol, verapamil, diltiazem, EPI, and NEPI levels; and serum chemistry values for groups H, HP, HV, HVP HD, and HDP for study period 2 (lower levels of verapamil and diltiazem) are given in table 2. There were no statistical differences in the plasma verapamil levels between groups HV and HVP, or in the plasma diltiazem levels between groups HD and HDP, during study periods 1 or 2. There was no difference in plasma propranolol levels between groups HP, HVP, and HDP during study period 2. Significant prolongation of the PR interval was seen as expected with both calcium channel blockers at the lower plasma levels tested in this study. With verapamil, the prolongation was exacerbated by the addition of propranolol. Propranolol, verapamil, and diltiazem alone had minimal effects upon the variables shown, except for a slight decrease in cardiac index and increase in SVR in the propranolol-alone group in the presence of halothane. When the propranolol was added to the lower levels of verapamil or diltiazem, SVR was increased, and HR, LV dP/dt, and CI were decreased. In the low verapamil + propranolol group, MAP was also decreased, PAO increased, and NEPI and EPI levels were elevated.

Hemodynamic values; PR interval of the ECG; plasma propranolol, verapamil, diltiazem, EPI, and NEPI levels; and serum chemistry values for groups H, HP, HV, and HD for study period 3 (higher levels of verapamil and diltiazem) are given in table 3, showing no effects of the propranolol alone, and minimal hemodynamic effects of the higher levels diltiazem alone. One of the animals in the HV group and two in the HD group developed atrioventricular conduction block. Mean plasma NEPI levels were increased in both groups, and the mean plasma EPI level was increased in the HV group. When the attempt was made to proceed to study period 3 in the HVP and HDP groups by increasing the verapamil or diltiazem infusion rates, the experiments had to be aborted in all six of the animals in the HVP group and 4/6 of the HDP animals because of severe hypotension (MAP < 50 mmHg), usually accompanied by 2° or higher heart block. At that point, CI was extremely low, SVR was high, and catecholamine levels were also high.

The semi-logarithmic plots of the isoproterenol dose *versus* the maximal change in heart rate for group H for the control isoproterenol dose response test and periods 1, 2, and 3 are shown in figure 2. The mean dose of isoproterenol required to cause an increase in HR of 40 beats per minute at control was 0.063 ± 0.014 $\mu g \cdot kg^{-1}$; in period 1, was 0.045 ± 0.005 $\mu g \cdot kg^{-1}$; in period 2, was 0.036 ± 0.006 $\mu g \cdot kg^{-1}$; and, in period 3, was 0.029 ± 0.006 $\mu g \cdot kg^{-1}$. The only statistically significant difference among all of the four values was that the mean dose required during period 3 was less than that required at

TABLE 3. Cardiovascular and Arterial Serum Chemistry Values and Plasma Levels of NEPI, EPI, Propranolol, Verapamil, and Diltiazem for Period 3 for Groups H (Halothane Only); HP (Halothane + Propranolol); HV (Halothane + High Verapamil); and HD (Halothane + High Diltiazem)

	Period 3			
	H	HP	HV	HD
n	5	6	6	5
HR (bpm)	120 ± 8	112 ± 7	106 ± 8	104 ± 10
MAP (mmHg)	98 ± 3	96 ± 5	75 ± 7*	86 ± 9
RA (mmHg)	5 ± 2	2 ± 1	8 ± 2	9 ± 2
PAO (mmHg)	8 ± 1	7 ± 1	12 ± 2*	9 ± 1
LV dP/dt (mmHg·s^{-1})	1910 ± 151	1392 ± 91	1125 ± 140*	1410 ± 206
CI (l·min^{-1}·m^{-2})	4.78 ± 0.49	4.22 ± 0.48	3.24 ± 0.63	3.61 ± 1.02
SVR (dynes·s·cm^{-5})	1993 ± 297	2272 ± 296	2223 ± 502	2305 ± 346
PR Interval (ms)	124 ± 5	143 ± 9	195 ± 29*†	209 ± 30*‡
Arterial pH	7.36 ± 0.02	7.37 ± 0.02	7.38 ± 0.02	7.40 ± 0.03
PaO_2 (mmHg)	175 ± 14	180 ± 10	178 ± 15	169 ± 1
$PaCO_2$ (mmHg)	34 ± 2	32 ± 1	33 ± 2	33 ± 2
[Na^+] (mEq·l^{-1})	144 ± 2	144 ± 1	145 ± 2	148 ± 2
[K^+] (mEq·l^{-1})	3.7 ± 0.1	3.7 ± 0.1	3.7 ± 0.1	3.8 ± 0.1
[Cl^-] (mEq·l^{-1})	108 ± 2	110 ± 1	113 ± 3	113 ± 2
[Ca^{++}] (mM·l^{-1})	1.94 ± 0.08	2.01 ± 0.05	1.85 ± 0.06	1.88 ± 0.06
Glucose (mg%)	115 ± 5	109 ± 5	135 ± 15	110 ± 5
Temperature (°C)	39.0 ± 0.2	39.1 ± 0.1	38.6 ± 0.3	38.9 ± 0.1
NEPI (pg·ml^{-1})	145 ± 36	125 ± 32	739 ± 310*	418 ± 44*
EPI (pg·ml^{-1})	302 ± 131	150 ± 31	1871 ± 484*	1068 ± 361
Drug levels (ng·ml^{-1})	—	50 ± 10	258 ± 17	326 ± 46

Mean ± SEM.
* = $P < 0.05$ compared to halothane.
† n = 5 (one animal with atrioventricular (AV) block).
‡ n = 4 (2 animals with AV block).

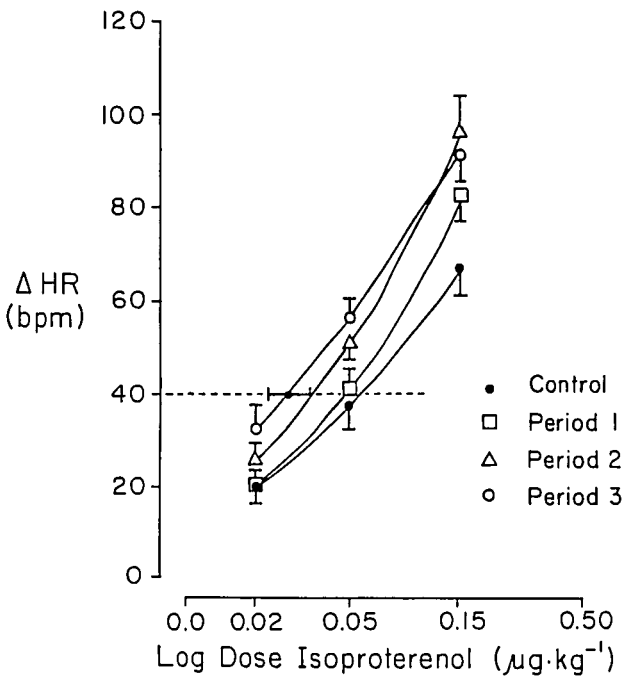

FIG. 2. Semilogarithmic plot of the isoproterenol dose *versus* the means of the maximal change in heart rate for group H (halothane only) for the control isoproterenol dose response test and for periods 1, 2, and 3. Heart rate values interpolated from the individual double reciprocal plots (see text). CD_{40} values indicated. Error bars omitted from CD_{40} values for control and periods 1 and 2 for clarity (values given in the text). The only statistically significant difference among the CD_{40} values was that the value during period 3 was less than that at control.

control. Fortunately, with this study design, time-matched comparisons with other groups could be made.

The isoproterenol dose *versus* heart rate change curves are shown for period 2 for groups H, HP, HV, and HVP in figure 3, and for groups H, HP, HD, and HDP in figure 4. The straight central portions of the isoproterenol dose-response curves were shifted towards higher isoproterenol doses for the same change in heart rate by both verapamil and diltiazem, as well as by propranolol. All CD_{40} values in figure 4 were significantly different from each other. In figure 3, all CD_{40} values were different from each other, with the exception that the value for the HVP group was not significantly different from that for the HP group. The curves for high verapamil and high diltiazem alone were similar to the low-dose curves; therefore, for clarity, only the low-dose curves are shown in the figures. No conclusions can be drawn about the maximal possible heart rate from this data. After the addition of propranolol to either low verapamil or low diltiazem, 40 times more isoproterenol was required to increase the heart rate by 40 beats per minute with either calcium channel blocker + propranolol combination, compared to the isoproterenol dose required in the presence of only halothane at the comparable time period.

Discussion

The model used for the present study was remarkably stable over the course of the experiments, as observed

with group H (Table 1). Even the effects of the isoproterenol response tests were transient, and values 20 min following the test were equivalent to values immediately prior to the test. While complete isoproterenol dose-response curves were not generated by this protocol (maximum heart rates obtainable under the various drug conditions not defined), shifts of the straight central portion of the curves away from the halothane-only curve could be observed.

The findings for the individual drugs when administered alone in the presence of halothane were consistent with the current understanding of their interactions with inhalation anesthetics. Propranolol, presumably by virtue of its ability to block peripheral beta receptors, when given alone resulted an increase in SVR and a decrease in CI; MAP was maintained without an increase in PAO or RA at these plasma levels. These findings are consistent with those of Roberts *et al.*, who noted that propranolol pretreatment in amounts which increased the isoproterenol requirements 30-fold for the same change in heart rate

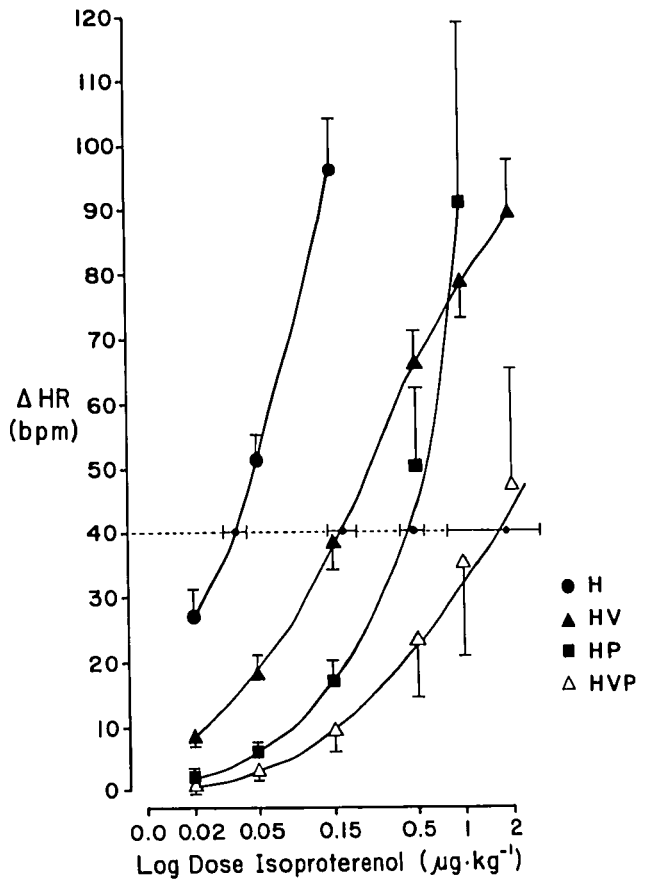

FIG. 3. Semilogarithmic plot of the isoproterenol dose *versus* the means of the maximal change in heart rate for groups H, HP, HV and HVP for period 2. Heart rate values interpolated from the individual double reciprocal plots (see text). CD_{40} values indicated. All CD_{40} values were statistically different from each other, with the exception that the value for HVP was no different from that for HP.

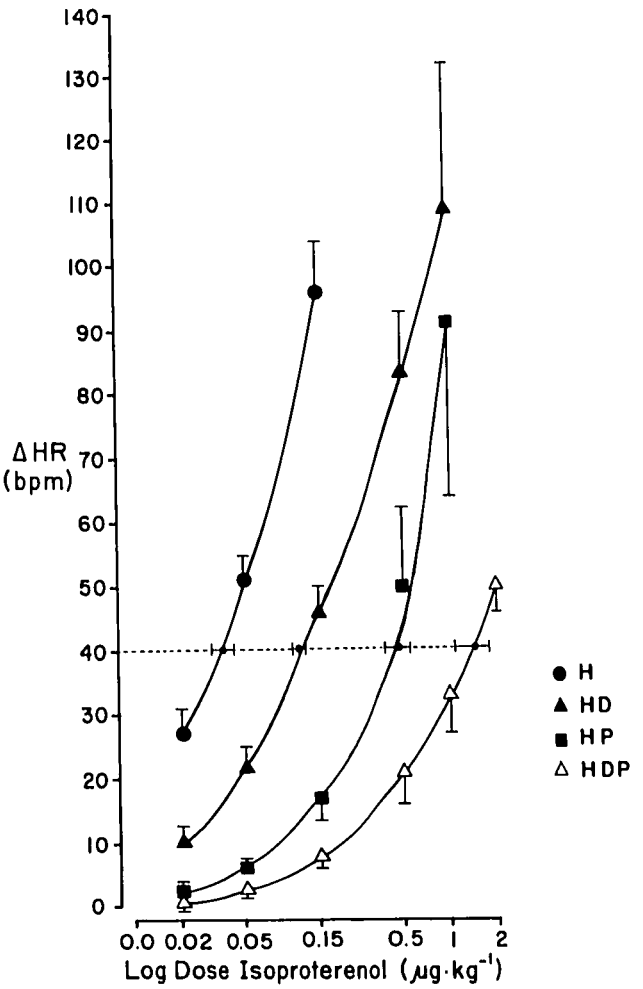

FIG. 4. Semilogarithmic plot of the isoproterenol dose *versus* the means of the maximal change in heart rate for groups H, HP, HD, and HDP for period 2. Heart rate values interpolated from the individual double reciprocal plots (see text). CD_{40} values indicated. All CD_{40} values were statistically different from each other.

caused only a minor degree of cardiac depression in healthy, normocapnic, halothane-anesthetized dogs.[20] Earlier investigations of the acute intravenous administration of propranolol to healthy, normovolemic dogs anesthetized with 1.5% halothane also demonstrated no change in MAP, but a modest reduction in aortic flow rates.[21] Diltiazem and verapamil, by virtue of their ability to interfere with slow-channel mediated calcium influx in the atrioventricular node, caused a prolongation of intracardiac conduction. No decrease in SVR was seen, consistent with other studies of continuous infusions of these drugs in the presence of inhalation anesthetics.[12,13,22] Perhaps as a result of the lack of vasodilation, no signs of compensatory reflex activity (increased HR, CI, or LV dP/dt) were observed. Though some increases in NEPI and EPI did occur with the calcium channel blocking drugs alone, because of intra-animal variability, the mean values for NEPI and EPI were not statistically different

from group H at period 2, for the low levels of verapamil or diltiazem. Despite the relatively benign hemodynamic effects with the calcium channel blocking drugs alone in the present study, the isoproterenol dose-response curves did reveal an impaired ability to respond to a beta adrenergic agonist, even in the presence of only a calcium channel blocker.

The importance of the choice of anesthetic is apparent when comparing these findings to those from a similar protocol during pentobarbital anesthesia.[23] In the presence of pentobarbital instead of halothane in the same animal model, a significant decrease in SVR occurred upon administration of verapamil or diltiazem alone, accompanied by significant increases in HR, LV dP/dt, and CI. During pentobarbital anesthesia, the addition of propranolol ablated the increases in HR, LV dP/dt, and CI that had occurred with calcium channel blocking drugs alone. The resulting hemodynamic values from a combined block at the lower verapamil and diltiazem levels were generally comparable to the anesthetic-alone group at the equivalent time.[23] In the current study in the presence of halothane, hemodynamic function was unchanged upon the administration of low doses of calcium channel blocking drugs, and very much worse upon the addition of propranolol. The addition of propranolol to the low-dose verapamil group resulted in decreased heart rate and increased PR interval. Increased SVR combined with depressed myocardial function resulted in decreased cardiac performance. The isoproterenol dose response tests confirmed that even very elevated levels of beta agonist would have a diminished effect in the presence of a combined blockade.

Of interest in the present study was that the higher infusion rates of verapamil and diltiazem that were tolerated alone, without difficulty, in the presence of anesthetic concentrations of halothane were toxic in the presence of an otherwise benign infusion of propranolol. The effects observed with propranolol and the low plasma levels of calcium channel blocking drugs were presumably enhanced when the calcium channel blocker levels were raised in the presence of propranolol. Even when the high doses of verapamil were given alone, NEPI and EPI levels were elevated in many animals, an indicator of an endogenous compensatory response that was not otherwise apparent from the hemodynamic values.

An interesting finding of this study was the somewhat more deleterious results in the HVP animals compared to the HDP group, when propranolol was added to the calcium channel blocking drugs. These findings included decreased MAP, increased PAO and PR interval, and marked increase in circulating catecholamine levels with low dose verapamil + propranolol, not seen with the lower dose of diltiazem + propranolol, as well as the fact that none of the verapamil dogs could tolerate the high-dose calcium blocker with propranolol. While one cannot rule out intrinsic differences between the groups of dogs, control values in this study were similar. The plasma levels at which interference with conduction occur are similar for either verapamil or diltiazem in healthy anesthetized dogs; however, the plasma levels at which hemodynamic impairment occurs is somewhat higher for diltiazem than verapamil.[12,13,22] The high circulating catecholamine levels which were observed in the verapamil + propranolol dogs were invariably associated with a poor outcome. This cannot entirely be explained by the isoproterenol dose-response curves generated for the two calcium channel blockers when given alone in this study. At low doses, the central portions of the curves for the two calcium channel blockers were similar. If anything, the absolute values for the verapamil plasma levels were less than the diltiazem levels. This perhaps indicates a smaller margin of safety regarding tolerable calcium channel blocker plasma levels if propranolol were to be added to verapamil during halothane anesthesia, as compared to adding propranolol to diltiazem under similar conditions. This is consistent with the finding of Kates *et al.*, who compared the hemodynamic effects of diltiazem and verapamil in halothane-anesthetized swine.[13] Instead of attempting to achieve similar plasma levels as was done in this study, the endpoint of their study was an equivalent degree of hypotension. They found that it took very much higher levels of diltiazem than verapamil to lower blood pressure by 25–30%.

The present study combined the intravenous administration of propranolol with either verapamil or diltiazem in healthy halothane-anesthetized dogs, at plasma levels of the latter two drugs that, alone, were within the range that produced electrophysiologic changes without major hemodynamic effects. The drug combinations resulted in a deleterious outcome, even at the lower calcium blocker levels (100 and 140 $ng \cdot ml^{-1}$ for verapamil and diltiazem, respectively). At the higher calcium blocker levels achieved in this study, which were at the upper end of the therapeutic range in man, the addition of propranolol resulted in severe hypotension, and 2° or higher heart block occurred. The extrapolation of animal findings to the clinical setting is limited because of species differences, the uncontrolled nature of the clinical setting, the presence of adjuvant drugs in patients, the use of different anesthetic concentrations, and the presence of impaired ventricular function, to name a few. Nevertheless, the results of this study would suggest that the concomitant intravenous administration of a beta blocker with verapamil or diltiazem be approached with extreme caution in the presence of inhalation anesthetics.

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