Anesthesiology
66:792–797, 1987

Amrinone and Verapamil-propranolol Induced Cardiac Depression during Isoflurane Anesthesia in Dogs

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This study was designed to investigate the possibility of whether verapamil diminishes the effects of amrinone, whether amrinone can reverse verapamil-propranolol depression, and also to evaluate whether the order of administering the drugs would have any effect during 1.7–1.8% end-tidal isoflurane anesthesia in dogs. At 3–4-week intervals, each of six conditioned mongrel dogs (23 ± 1 kg) received amrinone (A) (4 mg/kg plus 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$), verapamil (V) (200 μg/kg plus 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and propranolol (P) (150 μg/kg plus 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in four different orders of administration: VAP, AVP, VPA, and PVA. Plasma levels achieved were 15 ± 1 to 24 ± 2 μg/ml for amrinone, 24 ± 2 to 59 ± 10 ng/ml for propranolol, and 81 ± 10 to 163 ± 17 ng/ml for verapamil, equivalent to high therapeutic (amrinone) and therapeutic (propranolol, verapamil) levels in humans. The results of this study show that amrinone is able to reverse many of the effects of verapamil (group VAP) and also many of the effects of verapamil-propranolol or propranolol-verapamil (groups VPA, PVA) combinations. Amrinone improved cardiac index, left ventricular dP/dt_{max}, pulmonary capillary wedge pressure, and central venous pressure without increasing catecholamines. However, mean arterial pressure remained decreased with decreased systemic vascular resistance, which necessitates careful consideration depending upon patient circumstances. The results also show that verapamil-propranolol can reverse the positive inotropic effects of amrinone (group AVP). The authors conclude that amrinone is of therapeutic value for the reversal of untoward effects of potent cardiodepressant drugs, such as verapamil and propranolol, even in the presence of inhalation anesthetics. (Key words: Anesthetics: volatile; isoflurane. Heart: cardiac depression; contractility. Ions: calcium. Pharmacology: amrinone; propranolol; verapamil.)

INCREASED CALCIUM INFLUX through the voltage sensitive calcium channel contributes to the observed cardiovascular stimulatory effects of both catecholamines and phosphodiesterase inhibitors such as amrinone. Both of these classes of drugs increase intracellular levels of cyclic AMP which, by phosphorylating the channel proteins, increases the number of channels that are in the proper configuration to permit calcium influx.[1] These actions can be opposed by either beta adrenergic blocking drugs, which reduce the amount of cyclic AMP available, or by calcium channel blocking drugs, which inhibit the function of the phosphorylated channels. Verapamil has been shown to inhibit the toxic effects of aminophylline, another phosphodiesterase inhibitor,[2] and amrinone has been shown to oppose cardiovascular effects of verapamil in several animal models.[3,4]

Effects of inhalation anesthetics are additive with both calcium channel and beta blocking drugs, and may increase the risks of administering the latter drugs.[5,6] The combination of verapamil plus propranolol is particularly depressant during inhalation anesthesia.[7,8] Amrinone has been shown to reverse the depressant effects of inhalation anesthesia.[9,10] Whether amrinone can pharmacologically overcome the combined cardiodepressant effects of a beta blocker, a calcium channel blocker, and an inhalation anesthetic has never been investigated.

The present study was designed to systematically investigate the interactions of a representative beta blocker, propranolol; a calcium channel blocker, verapamil; and a bipyridine cardiotonic, amrinone, in a well-established animal model during inhalation anesthesia[9,11] at plasma levels of each that are pharmacodynamically active but not toxic.

Methods

The experimental protocol was approved by the institutional Animal Research Committee. At 3–4-week intervals, each of four experiments were carried out in six conditioned mongrel dogs of either sex, weighing 23 ± 1 kg (mean ± SEM), and cared for in accordance with the American Association for Accreditation of Laboratory Animal Care. In each experiment, the animal received a combination of three drugs: amrinone (A), verapamil (V), and propranolol (P) during isoflurane anesthesia with the order of drug administration varying for the four experiments. The groups were: verapamil-amrinone-propranolol (VAP), amrinone-verapamil-propranolol (AVP), verapamil-propranolol-amrinone (VPA), and propranolol-verapamil-amrinone (PVA). The order of the experiments was random. The dogs were anesthetized with 1.7–1.8% end-tidal isoflurane in 40% oxygen in air *via* a chronic tracheostomy and mechanically ventilated (Harvard Apparatus Company, Model 623), to maintain Pa_{CO_2} within normal limits as determined by serial arterial blood gas measurements every 30 min during each experiment (Instrumentation Laboratories Analyzer Model 813). $NaHCO_3$ was administered as needed to maintain *p*H within normal limits, and NaCl 0.9% was infused intravenously at approximately 8 $ml \cdot kg^{-1} \cdot h^{-1}$ to maintain adequate hydration and urine output. Temperature was

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Received from the Department of Anesthesiology, UCLA School of Medicine, Los Angeles, California. Accepted for publication January 28, 1987.

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maintained between 38° C and 39° C with a warming blanket and a heating lamp. End-tidal concentrations of isoflurane, CO_2 and O_2 were continuously measured by mass spectrometry (Perkin-Elmer, Model # MGA 1100). An arterial catheter was placed in a femoral artery for direct blood pressure measurements and blood sampling. A pulmonary artery catheter was passed *via* an external jugular vein for measurements of right atrial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP), and cardiac output (CO); the latter in triplicate by thermodilution (Edwards Laboratory Cardiac Output Computer, Model 9520). A micromanometer-tipped catheter (Millar Instruments, Inc. Model PC 350) was placed retrogradely in the left ventricle (LV), *via* a femoral artery, for direct LV pressure measurements and electronic derivation of LV dP/dt. The maximum LV dP/dt (LV dP/dt_{max}) was taken as the peak positive deflection of the LV dP/dt trace. Limb lead II of the electrocardiogram (ECG), heart rate (HR), arterial blood pressure, central venous pressure (CVP), pulmonary arterial pressure, LV pressure, and LV dP/dt were continuously recorded on a Hewlett Packard polygraph, Model 7758A. In addition, the ECG was intermittently recorded at fast paper speed (100 mm/s) for measurement of PR intervals. Systemic and pulmonary vascular resistances, cardiac index, stroke volume index, and stroke work index were calculated (SVR, PVR, CI, SVI, SWI). The blood samples were analyzed for plasma concentrations of epinephrine (EPI), norepinephrine (NEPI), amrinone, verapamil, and propranolol by high performance liquid chromatography.[12-14]

After 60 min of stabilization with 1.7–1.8% end-tidal isoflurane, the experiments consisted of four 30-min periods of drug administration and two additional 30-min periods for recovery after cessation of all drugs. Baseline cardiovascular measurements were made and blood samples taken. The loading dose of the first drug for that experiment was given and an infusion started at the same time. After 30 min of the first drug, the loading dose of the second drug was given and its infusion started. After 30 min of the combination of the first and second drugs, the loading dose of the third drug was given and the three drugs were given together for two consecutive 30-min periods. All drug infusions were then discontinued. Measurements and blood samples were repeated at 25 and 30 min of each 30-min drug administration period, and also at 25, 30, 55, and 60 min of recovery. The loading doses and infusion rates were: amrinone, 4 mg/kg over 2 min followed by 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$, verapamil, 200 μg/kg over 5 min followed by 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$; and propranolol, 150 μg/kg over 5 min, followed by 0.8 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All drugs were freshly prepared the day of the experiment. Propranolol and verapamil were dissolved in 0.9% NaCl in concentrations of 60 μg/ml and 500 μg/ml, respectively. The amrinone solvent used has previously been shown to have no statistically significant effect on hemodynamic parameters in a similar model in the same laboratory.[9,11] Blood samples for measurements of serum levels of potassium, sodium, calcium, chloride, glucose, and hematocrit were taken three times during each experiment: at baseline, 90 min after baseline measurements, and at the time of the final measurements.

Intragroup differences were examined by analysis of variance for repeated measures and intergroup differences by analysis of variance. Bonferroni modified *t* tests were used when analysis of variance for repeated measures or analysis of variance indicated a significant difference. A *P* value of less than 0.05 was considered statistically significant.

Results

There were no differences in any variable at the time of baseline measurements among groups VAP, AVP, VPA, and PVA, or among the 25- and 30-min values for any variable in any group for any of the measurement periods. The end-tidal isoflurane concentrations (1.7–1.8%) were stable over time in each group and equivalent among the groups. Since there were no statistically significant differences in the mean 25- and 30-min values, indicating a relatively stable condition at the time of measurements, the 30-min values were used for statistical comparisons and for the tables.

Baseline and successive 30-min values for hemodynamic parameters are shown in table 1, plasma EPI and NEPI levels in table 2, and plasma drug levels for amrinone, propranolol, and verapamil in table 3. In almost all cases, there were no significant differences between the two 30-min periods of the three drugs together in any group (90-min values = 120-min values). It can be seen in table 3 that very similar plasma levels for each drug were obtained among the four groups.

Verapamil Alone

When compared to baseline values, verapamil alone (88 ± 8 and 104 ± 6 ng/ml in VAP and VPA, respectively) caused an increase in PR interval and a decrease in MAP, LV dP/dt_{max}, and SWI, and in addition, in VPA, verapamil also increased CVP.

Amrinone Alone

At a plasma concentration of 15 ± 1 μg/ml amrinone alone in AVP increased LV dP/dt_{max} and HR, and decreased CVP, PCWP, SWI, SVR, and MAP when compared to baseline values.

TABLE 1. Cardiovascular Values for Verapamil-amrinone-propranolol (VAP), Amrinone-verapamil-propranolol (AVP), Verapamil-propranolol-amrinone (VPA), and Propranolol-verapamil-amrinone (PVA) Groups

Group	Baseline	Drug 1, 30 min	Drug 1 & 2, 60 min	Drug 1 & 2 & 3		Recovery	
				90 min	120 min	30 min	60 min
HR (bpm)							
VAP	126 ± 6	V 122 ± 5	VA 131 ± 6	VAP 115 ± 8*	115 ± 7	116 ± 5	110 ± 8†
AVP	131 ± 4	A 152 ± 7*	AV 141 ± 7	AVP 124 ± 9	118 ± 8	113 ± 7	111 ± 7
VPA	128 ± 9	V 121 ± 7	VP 96 ± 10*†	VPA 109 ± 9	108 ± 8†	108 ± 7†	105 ± 8†
PVA	122 ± 9	P 119 ± 9	PV 109 ± 8	PVA 116 ± 9	116 ± 9	114 ± 9	113 ± 4
PR (ms)							
VAP	117 ± 6	V 153 ± 10*	VA 135 ± 10	VAP 151 ± 15†	150 ± 11†	133 ± 6	123 ± 5
AVP	118 ± 4	A 101 ± 2	AV 131 ± 8*	AVP 152 ± 13†	162 ± 17†	133 ± 11*	128 ± 7
VPA	113 ± 10	V 153 ± 8*	VP 197 ± 12*†	VPA 161 ± 16*†	165 ± 16†	133 ± 7	130 ± 6
PVA	125 ± 10	P 122 ± 6	PV 162 ± 10*†	PVA 137 ± 13	146 ± 15	128 ± 7	121 ± 4
MAP (mmHg)							
VAP	90 ± 6	V 72 ± 2*	VA 58 ± 2*†	VAP 60 ± 3†	60 ± 3†	78 ± 4*†	86 ± 4
AVP	93 ± 2	A 75 ± 3*	AV 65 ± 4*†	AVP 66 ± 3†	68 ± 3†	80 ± 3*†	86 ± 2
VPA	93 ± 6	V 77 ± 4*	VP 69 ± 8†	VPA 65 ± 4†	65 ± 4†	79 ± 3*†	85 ± 3
PVA	93 ± 4	P 92 ± 5	PV 82 ± 5†	PVA 73 ± 3†	71 ± 2†	85 ± 2*	94 ± 5
CVP (mmHg)							
VAP	4.7 ± 0.5	V 6.0 ± 0.7	VA 3.5 ± 0.6*	VAP 4.3 ± 0.9	4.0 ± 1.0	3.3 ± 0.7	3.0 ± 0.7
AVP	4.4 ± 0.4	A 2.7 ± 0.4*	AV 4.1 ± 0.8*	AVP 4.0 ± 0.5	4.0 ± 0.6	3.5 ± 0.6	3.2 ± 0.7
VPA	4.1 ± 0.4	V 6.1 ± 0.6*	VP 8.0 ± 1.2*†	VPA 4.1 ± 0.6*	4.5 ± 0.9	3.9 ± 0.9	3.6 ± 0.7
PVA	4.3 ± 0.5	P 3.6 ± 0.5	PV 6.3 ± 1.0*†	PVA 3.0 ± 0.6*†	3.2 ± 0.6	2.5 ± 0.5†	2.6 ± 0.7†
PCWP (mmHg)							
VAP	7.7 ± 0.6	V 9.2 ± 0.9	VA 5.8 ± 0.4*	VAP 7.1 ± 0.7	7.1 ± 0.8	6.1 ± 0.7	6.0 ± 0.5
AVP	7.3 ± 0.6	A 4.1 ± 0.4*	AV 5.4 ± 0.5†	AVP 7.4 ± 0.4*	6.8 ± 0.6	6.2 ± 0.5	6.3 ± 0.6
VPA	7.3 ± 0.6	V 9.1 ± 1.0	VP 10.8 ± 0.6†	VPA 6.9 ± 0.9*	7.1 ± 1.1	6.2 ± 0.9	6.5 ± 0.8
PVA	7.4 ± 0.6	P 7.2 ± 0.4	PV 10.2 ± 0.8*†	PVA 5.6 ± 0.2*†	5.4 ± 0.4†	4.8 ± 0.2†	5.1 ± 0.1†
LV dP/dt_{max} ($mmHg \cdot s^{-1}$)							
VAP	2442 ± 128	V 1817 ± 193*	VA 3433 ± 297*†	VAP 2350 ± 206*	2308 ± 192	2496 ± 164	2483 ± 138
AVP	2529 ± 174	A 4467 ± 686*	AV 4217 ± 543†	AVP 2638 ± 209*	2350 ± 163	2492 ± 214	2571 ± 193
VPA	2447 ± 86	V 1834 ± 195*	VP 982 ± 70*†	VPA 1801 ± 163*†	1808 ± 208†	1840 ± 144†	1916 ± 95†
PVA	2457 ± 221	P 2054 ± 116	PV 1190 ± 75*†	PVA 2145 ± 207*	2161 ± 191	2254 ± 154	2202 ± 124
CI ($l \cdot min^{-1} \cdot m^{-2}$)							
VAP	5.6 ± 0.6	V 4.7 ± 0.4	VA 6.9 ± 0.7*	VAP 4.9 ± 0.4*	4.9 ± 0.4	4.7 ± 0.3	4.2 ± 0.5†
AVP	5.3 ± 0.6	A 6.1 ± 1.0	AV 6.8 ± 0.7†	AVP 4.9 ± 0.7*	4.2 ± 0.5	4.0 ± 0.5	3.9 ± 0.5
VPA	5.3 ± 0.6	V 4.4 ± 0.5	VP 1.9 ± 0.3*†	VPA 3.3 ± 0.4*†	3.1 ± 0.4†	3.0 ± 0.3†	2.9 ± 0.4†
PVA	5.4 ± 0.6	P 4.2 ± 0.3*	PV 2.7 ± 0.3*†	PVA 3.7 ± 0.3†	3.9 ± 0.4†	3.5 ± 0.6†	3.4 ± 0.5†
SVI ($ml \cdot m^{-2}$)							
VAP	45 ± 4	V 39 ± 5	VA 52 ± 4*	VAP 43 ± 3	43 ± 3	41 ± 3	38 ± 3
AVP	40 ± 4	A 39 ± 4	AV 48 ± 4*	AVP 39 ± 4*	36 ± 3	35 ± 3	35 ± 3
VPA	42 ± 3	V 37 ± 5	VP 20 ± 3*†	VPA 31 ± 3*†	29 ± 3†	28 ± 2†	28 ± 3†
PVA	45 ± 6	P 36 ± 4*	PV 26 ± 3*†	PVA 33 ± 4*†	35 ± 4†	32 ± 6†	30 ± 4†
SWI ($g \cdot m \cdot m^{-2}$)							
VAP	51 ± 7	V 33 ± 3*	VA 37 ± 3†	VAP 31 ± 2†	31 ± 3†	39 ± 2†	41 ± 3
AVP	47 ± 5	A 38 ± 5*	AV 40 ± 5	AVP 31 ± 4*†	30 ± 3†	36 ± 4†	38 ± 3†
VPA	48 ± 5	V 34 ± 5*	VP 16 ± 4*†	VPA 24 ± 3†	23 ± 3†	28 ± 3†	30 ± 3†
PVA	52 ± 7	P 42 ± 6*	PV 25 ± 6*†	PVA 30 ± 3†	31 ± 4†	35 ± 7†	37 ± 6†
SVR ($dynes \cdot s \cdot cm^{-5}$)							
VAP	1442 ± 189	V 1352 ± 162	VA 751 ± 88*†	VAP 1045 ± 95	1066 ± 105	1480 ± 175	1966 ± 347†
AVP	1605 ± 176	A 1166 ± 138*	AV 830 ± 74†	AVP 1227 ± 154	1441 ± 179	1814 ± 227	2035 ± 258†
VPA	1595 ± 228	V 1556 ± 215	VP 2960 ± 278*†	VPA 1702 ± 175*	1811 ± 165	2320 ± 280†	2672 ± 346†
PVA	1577 ± 173	P 1949 ± 129	PV 2575 ± 148†	PVA 1728 ± 90	1627 ± 116	2597 ± 650*†	2627 ± 293†
PVR ($dynes \cdot s \cdot cm^{-5}$)							
VAP	149 ± 16	V 176 ± 17	VA 138 ± 9*	VAP 143 ± 11	134 ± 15	154 ± 13	171 ± 17
AVP	152 ± 15	A 142 ± 18	AV 125 ± 11	AVP 130 ± 15	156 ± 14	151 ± 21	152 ± 14
VPA	151 ± 13	V 175 ± 12	VP 205 ± 21	VPA 169 ± 20	184 ± 19	196 ± 13	209 ± 13
PVA	151 ± 21	P 178 ± 23	PV 172 ± 13	PVA 180 ± 18	180 ± 21	212 ± 60	194 ± 33

Mean ± SEM.

* $P < 0.05$ compared to previous value for that same group.

† $P < 0.05$ compared to the baseline value for that same group.

TABLE 2. Epinephrine (EPI) and Norepinephrine (NEPI) Plasma Levels for VAP, AVP, VPA, and PVA Groups

Group	Baseline	Drug 1, 30 min	Drug 1 & 2 60 min	Drug 1 & 2 & 3 90 min	Drug 1 & 2 & 3 120 min	Recovery 30 min	Recovery 60 min
EPI (pg · ml^{-1})							
VAP	352 ± 99	V 571 ± 180	VA 546 ± 184	VAP 392 ± 134	342 ± 87	142 ± 29	102 ± 21
AVP	346 ± 109	A 360 ± 97	AV 759 ± 273	AVP 559 ± 275	382 ± 155	184 ± 63	96 ± 42
VPA	525 ± 108	V 836 ± 154	VP 2608 ± 1495†	VPA 783 ± 205	937 ± 284	425 ± 120	313 ± 92
PVA	386 ± 150	P 349 ± 129	PV 794 ± 230*†	PVA 429 ± 158*	432 ± 155	247 ± 90	217 ± 108
NEPI (pg · ml^{-1})							
VAP	108 ± 13	V 187 ± 53	VA 167 ± 41	VAP 233 ± 61	243 ± 66†	114 ± 21*	87 ± 10
AVP	88 ± 16	A 87 ± 23	AV 236 ± 63	AVP 206 ± 43	381 ± 170†	93 ± 15*	65 ± 17
VPA	132 ± 12	V 182 ± 22	VP 382 ± 131†	VPA 200 ± 24	260 ± 39	148 ± 19	116 ± 15
PVA	108 ± 19	P 87 ± 15	PV 157 ± 24*	PVA 134 ± 22	153 ± 30	93 ± 19*	99 ± 19

Mean ± SEM.
* $P < 0.05$ compared to previous value for that same group.
† $P < 0.05$ compared to the baseline value for that same group.

PROPRANOLOL ALONE

Propranolol alone at a plasma concentration of 30 ± 3 ng/ml in PVA decreased CI, SVI, and SWI.

VERAPAMIL FOLLOWED BY AMRINONE

Comparisons were made in group VAP between the values at 60 min and the values at 30 min (table 1). The addition of amrinone (16 ± 1 μg/ml) to verapamil (82 ± 6 ng/ml) in VAP reversed many of the effects of verapamil, increasing LV dP/dt_{max}, CI, and SVI, and decreasing CVP, PCWP, SVR, PVR, and MAP without any change in plasma catecholamine levels. *Propranolol* added to verapamil-amrinone (90-min measurement) reversed some of the effects of amrinone, decreasing HR, LV dP/dt_{max}, and CI.

AMRINONE FOLLOWED BY VERAPAMIL

Comparisons were made in group AVP between the values at 60 min and the values at 30 min. The addition of verapamil (81 ± 10 ng/ml) to amrinone (19 ± 2 μg/ml) reversed many of the beneficial effects of amrinone, increasing PR interval, CVP, and SVI, and decreased MAP further (75 ± 3 to 65 ± 4 mmHg). Adding *propranolol* to amrinone-verapamil (90-min measurement) worsened the hemodynamic status further, increasing PCWP and decreasing LV dP/dt_{max}, CI, and SWI.

VERAPAMIL-PROPRANOLOL COMBINATIONS

In groups VPA and PVA, the concomitant administration of verapamil and propranolol caused a severe cardiovascular depression in both groups at 60 min, with

TABLE 3. Amrinone (A), Propranolol (P), and Verapamil (V) Plasma Levels

Group	Drug 1, 30 min	Drug 1 & 2, 60 min	Drug 1 & 2 & 3 90 min	Drug 1 & 2 & 3 120 min	Recovery 30 min	Recovery 60 min
A (μg · ml^{-1})						
VAP		VA 16 ± 1	VAP 19 ± 1*	20 ± 1	15 ± 1*	12 ± 1
AVP	A 15 ± 1	AV 19 ± 2*	AVP 23 ± 2*	24 ± 2	18 ± 2*	14 ± 1*
VPA			VPA 16 ± 1	19 ± 1*	12 ± 1*	10 ± 1
PVA			PVA 16 ± 2	19 ± 1	13 ± 1*	11 ± 1
P (ng · ml^{-1})						
VAP			VAP 38 ± 2	32 ± 2*	18 ± 1*	15 ± 1
AVP			AVP 34 ± 4	32 ± 4	18 ± 2*	15 ± 2
VPA		VP 59 ± 10	VPA 40 ± 5*	37 ± 4	20 ± 3*	18 ± 3
PVA	P 30 ± 3	PV 29 ± 2	PVA 26 ± 2	24 ± 2	18 ± 2*	14 ± 2
V (ng · ml^{-1})						
VAP	V 88 ± 8	VA 92 ± 6	VAP 102 ± 5	113 ± 7	52 ± 4*	42 ± 5
AVP		AV 81 ± 10	AVP 105 ± 9*	124 ± 14	53 ± 5*	40 ± 4
VPA	V 104 ± 6	VP 163 ± 17*	VPA 134 ± 9	143 ± 11	63 ± 4*	50 ± 4
PVA		PV 113 ± 6	PVA 107 ± 7	114 ± 10	51 ± 7*	42 ± 6

Mean ± SEM.
* $P < 0.05$ compared to previous value for that same group.

decreased MAP, LV dP/dt_{max}, CI, SVI, SWI, and increased PR interval, CVP, PCWP, and SVR when compared to the baseline values. At 60 min, compared to baseline, EPI plasma levels were increased in both groups, and NEPI plasma levels were increased in group VPA. When 60-min values were compared to 30-min values, both EPI and NEPI plasma levels were increased in group PVA, while, in group VPA, catecholamines increased in 4/6 animals. At 60 min, when propranolol was added to verapamil, study conditions became unstable in group VPA associated with a sudden elevation of verapamil plasma level, as shown in table 3 (group VPA, 60 min).

Amrinone Added to Verapamil-Propranolol Combinations

Comparisons in groups VPA and PVA were made of the values at 90 min to the values at 60 min. In group VPA, verapamil and propranolol plasma levels were elevated as noted above at 60 min. Amrinone reversed many of the effects of concomitant administration of verapamil-propranolol, increasing LV dP/dt_{max} and SVI, and decreasing CVP and PCWP in both groups VPA and PVA. In addition, in group VPA, amrinone shortened PR interval, decreased SVR, and increased CI.

When the four groups were compared to each other at 90 min, when all three drugs were present in each group, there were no differences between them except for higher LV dP/dt_{max} in group AVP when compared to group VPA. SVR was also lower in group VAP when compared to groups VPA and PVA.

Recovery

Compared to the values at 120 min, 30 min after cessation of drug infusions, there was a significant increase in MAP in all the groups, and decrease in NEPI plasma levels in all the groups except for group VPA, as shown in tables 1 and 2. In addition, when compared to the values at 120 min, PR interval was shorter in group AVP, and SVR was higher in group PVA. The drug levels at this time are shown in table 3. MAP was equivalent to baseline 60 min after cessation of drug infusions.

Values for serum sodium, potassium, calcium, chloride, glucose, hematocrit, and arterial blood gases were within normal limits throughout the studies in all dogs. No arrhythmias or other evidence of amrinone toxicity were observed. One animal temporarily had third degree atrioventricular conduction block with these levels of verapamil and propranolol when studied for AVP, VPA, and PVA.

Discussion

The interpretation of these results must take into account that the effects of all three drugs vary with their plasma levels.[6,9,11,15] The plasma levels of verapamil achieved in this study were equivalent to the low therapeutic range in humans, and produced the expected prolongation of atrioventricular conduction and diminution of ventricular function and blood pressure in the presence of isoflurane.[6] The plasma propranolol levels are equivalent to those achieved in previous studies from the same laboratory, levels which produced marked rightward shifts in isoproterenol dose-heart rate response curves, yet had minimal effects alone on cardiovascular function.[7,8] The levels of amrinone achieved were higher than those used in previous studies for reversal of anesthetic-induced cardiovascular depression.[11] The elevated HR and increased LV dP/dt_{max} with these levels of amrinone alone were not associated with increased SWI; however, the effects of these levels of amrinone alone under conditions of limited coronary reserve were not tested. The effects of the verapamil-propranolol combinations are consistent with previous work in this laboratory[7,8] and others.[16] Hamann *et al.*[16] observed pharmacokinetic changes during combined propranolol-verapamil administration that perhaps account for the increased verapamil level after verapamil-propranolol in group VPA. Changes in hepatic blood flow caused by hemodynamic changes were correlated with increased verapamil concentration by Hamann in another study.[17] It is interesting to note in this study that, when amrinone was subsequently added to VP in VPA, CI improved, and both verapamil and propranolol plasma levels decreased, the latter to a statistically significant degree.

The results of this study show that amrinone is able to reverse many of the effects of verapamil (VAP) and, also, many of the effects of verapamil-propranolol and propranolol-verapamil combinations (VPA, PVA), even during 1.7–1.8% end-tidal isoflurane anesthesia in dogs. Amrinone did not prevent atrioventricular conduction from worsening when started before verapamil in AVP (table 1, 60 min). This study also demonstrated that the order of giving verapamil/propranolol or giving verapamil/amrinone made little difference in the hemodynamic effects achieved with these two drug pairs. Verapamil/propranolol negated the positive inotropic effects of amrinone and vice versa, such that the net effects of the three drugs together was equivalent, regardless of the order of administration.

Amrinone improved cardiac function without increasing circulating catecholamines, despite evidence of vasodilation. This is consistent with previous work during inhalation anesthesia.[9,11] Similar to previous work, even though CI, LV dP/dt_{max}, PCWP, and CVP were improved, MAP remained decreased after amrinone, associated with reduced SVR. Whether such a condition would be tolerated would depend on individual patient circumstances.

Thus, this study has shown that amrinone in sufficiently high levels is of therapeutic value for the reversal of untoward effects of pharmacologic interventions with potent cardiodepressant drugs, such as verapamil and propranolol, even in the presence of an inhalation anesthetic. These effects can be expected to be plasma-level dependent, and consideration must be made as to whether the improved cardiac output caused by amrinone can offset a possible reduced perfusion pressure in selected patients.

The authors thank Sterling-Winthrop Research Laboratories, Rensselaer, NY, for supplying the amrinone; Owen Buchea and Tom Patin for technical assistance; and Tony Law and Mercedes Espiritu for performing the plasma assays.

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