

Verapamil Worsens Rate of Development and Hemodynamic Effects of Acute Hyperkalemia in Halothane-anesthetized Dogs: Effects of Calcium Therapy

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The hemodynamic effects of verapamil pretreatment *versus* no pretreatment were evaluated in five acutely hyperkalemic dogs. Using ECG evidence for severe hyperkalemia, the halothane-anesthetized dogs were rendered acutely hyperkalemic to similar plasma levels of K^+ ($K^+ = 8.2 \pm 0.8$ mEq/l verapamil plus hyperkalemia, $K^+ = 9.4 \pm 0.2$ mEq/l hyperkalemic controls). The verapamil-hyperkalemic group had significantly lower cardiac indexes (CI) ($CI = 1.3 \pm 0.5$ l · min⁻¹ · m⁻² verapamil plus hyperkalemia *vs.* $CI = 3.0 \pm 0.2$ l · min⁻¹ · m⁻² hyperkalemic controls) and lower mean arterial pressures (MAP = 60 ± 13 mmHg verapamil plus hyperkalemia *vs.* MAP = 96 ± 7 mmHg hyperkalemic controls). Calcium therapy for hyperkalemia that returned CI to control levels in hyperkalemic controls only partially reversed the severe hemodynamic depression and did not improve the AV block seen during hyperkalemia in the presence of the calcium entry blocker verapamil. Surprisingly, the total mEq of KCl infused at the same rate into verapamil-pretreated dogs to result in similar high serum potassium levels was only one-third that required in dogs not pretreated with verapamil (1.6 ± 0.3 mEq/kg KCl in verapamil-hyperkalemia group *vs.* 5.0 ± 0.7 mEq/kg KCl in hyperkalemic controls). The authors conclude 1) verapamil renders hyperkalemia likely after much less intravenous K^+ administration; 2) the hemodynamic depression seen during acute hyperkalemia in halothane-anesthetized dogs is much more severe in the presence of verapamil; 3) calcium therapy is only partially effective in reversing the hemodynamic depression caused by hyperkalemia in the presence of the Ca^{++} entry blocker verapamil; 4) Ca^{++} in the dosage studied was not therapeutic for second-degree A-V block seen in the acutely hyperkalemic dog pretreated with verapamil and anesthetized with halothane. (Key words: Anesthetics, volatile; halothane. Heart: anti-arrhythmia agents, verapamil; myocardial function. Ions: calcium; potassium, hyperkalemia.)

VERAPAMIL INHIBITS slow inward calcium currents across excitable membranes.¹ The drug recently has been approved in the United States for intravenous treatment of supraventricular tachyarrhythmias and orally for angina pectoris. Increasing numbers of surgical patients now are receiving verapamil.

Verapamil¹⁻³ and halothane⁴⁻⁶ are both direct myocardial depressants and verapamil¹⁻³ also decreases peripheral vascular resistance. Verapamil,^{2,7,8} high concen-

trations of halothane,⁹ and hyperkalemia¹⁰⁻¹⁴ all prolong A-V nodal conduction. We therefore were concerned that halothane-anesthetized patients receiving verapamil might exhibit significant myocardial depression and A-V block if they became hyperkalemic. Clinically, hyperkalemia can occur during and after massive transfusion, intravenous potassium overdose, trauma, burns, and renal failure.^{12,13}

Calcium is standard immediate therapy for acute hyperkalemia.^{12,13,15} We were concerned about the efficacy of such Ca^{++} therapy in the face of the combination of hyperkalemia, halothane anesthesia, and calcium entry blockade. Accordingly, we studied hemodynamic and electrocardiographic effects of verapamil pretreatment in halothane-anesthetized dogs subsequently rendered acutely hyperkalemic. We then evaluated efficacy of calcium therapy for acute hyperkalemia without verapamil treatment *versus* with verapamil pretreatment.

Methods

Two separate experiments were done at least one week apart on each of five fasting mongrel dogs weighing 10.7 ± 0.4 kg (mean \pm SE) and anesthetized with steady state 1 MAC end-tidal halothane (Beckman® LB II analyzer; Beckman Instruments Inc., Fullerton, California). Succinylcholine (30 mg) was used to facilitate tracheal intubation and thereafter was infused continuously (100 mg/h) to provide muscle paralysis. Mechanical ventilation was maintained and Pa_{O_2} was held as close to 150 mmHg as possible by adjusting inspired O_2 and N_2 concentrations. Sodium bicarbonate was administered if buffer base was below 40 mEq/l.

Separate peripheral intravenous cannulas were placed for drug and fluid administration. The left common carotid artery was cannulated for blood sampling and for monitoring of mean arterial pressure (MAP). Using a left external jugular vein, a 5 Fr. catheter was placed in the pulmonary artery for measuring right atrial (RA), pulmonary artery (PA), pulmonary artery wedge pressure (PAWP), and thermal dilution cardiac output (CO), the latter with an Instrumentation Laboratories 701 Cardiac Output Computer® (Instrumentation Laboratory Inc., Lexington, Massachusetts). EKG was recorded on a Grass 810® recorder (Grass Instrument Co., Quincy, Massachusetts).

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TABLE 1. K⁺, Ca⁺⁺, and Hemodynamic Measurements in Dogs

	Serum K ⁺ mEq/l		Whole Blood Ionized Ca ⁺⁺ mEq/l		HR (BPM)	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Control	3.3 ± 0.1	3.5 ± 0.3	2.7 ± 0.1	2.6 ± 0.1	140 ± 10	116 ± 10
Postverapamil	—	3.3 ± 0.8	—	2.6 ± 0.2	—	124 ± 9
Prior to Ca ⁺⁺ therapy	9.4 ± 0.2*	8.2 ± 0.8*	2.9 ± 0.2	2.4 ± 0.1	106 ± 9	122 ± 18
1 min post Ca ⁺⁺ therapy	9.3 ± 0.2*	8.9 ± 2*	3.6 ± 0.2*	3.3 ± 0.3	180 ± 19	78 ± 24
5 min post Ca ⁺⁺ therapy	7.4 ± 0.5*	6.6 ± 0.7*	3.1 ± 0.1	3.4 ± 0.3*‡	154 ± 16†	86 ± 12†

N = 5, mean ± SEM

* Significant difference from control.

† Significant difference between Group 1 and Group 2.

‡ Between 1 and 5 min after calcium administration, three of five

verapamil-pretreated hyperkalemic dogs were given a second bolus of calcium (14 mg/kg) because of continuing severe hemodynamic depression.

Plasma (K⁺) and whole blood ionized Ca⁺⁺ were measured with a calibrated Clin-Ion® (Applied Medical Technology, Inc., Palo Alto, California) Cl-3 ion sensitive electrode. Urine production and urine (K⁺) also were measured in three animals. Plasma verapamil and norverapamil were measured by a modification of the procedure of Harapat and Kates.¹⁶ Verapamil, norverapamil, and an internal standard (D-517 from Knoll Pharmaceutical Company, Wippony, New Jersey) were extracted from alkalized serum (4:1 v/v, plasma 0.5 M NaOH) into diethyl ether. The drugs were then back-extracted into a small volume of dilute nitric acid (pH 2.5). The extract was chromatographed on a Beckman 5- μ m, 15 cm \times 4.6 mm ODS column with a mobile phase consisting of 30% acetonitrile in 0.1 M/l potassium phosphate containing 1% triethylamine. The endogenous fluorescence of each molecule was measured (ex. λ = 203 nm, em. λ = 320 nm) and used to quantitate each. Day-to-day reproducibility (N = 16) of this procedure was 4.7% for verapamil and 3.6% for norverapamil at 100 ng/ml.

After control hemodynamic and blood gas measurements were obtained, animals were given iv KCl, infused at 0.075 mEq \cdot kg⁻¹ \cdot min⁻¹. During one of the two separate studies in each dog, no verapamil was given (Group 1). In the other study, in each animal, verapamil 0.15 mg/kg bolus, plus a verapamil infusion of 5.6 μ g \cdot kg⁻¹ \cdot min⁻¹¹⁷ was given 10 min prior to beginning the KCl infusion (Group 2). The two studies in each dog were separated by at least 1 week and were performed in random order. Hemodynamic and blood gas measurements were repeated 10 min after the bolus of verapamil was given and every 10 min after the KCl infusion was begun. KCl was infused until ECG changes typical of severe hyperkalemia were seen.^{11,12,15} These consisted of tall peaked T waves, widened QRS, loss of P waves, "sine wave" QRS configuration, or severe second degree A-V block. Prior to calcium administration, hemodynamic recordings and blood samples for K⁺ and verapamil determinations were collected. Calcium chloride (14 mg/

kg)¹⁵ then was given as a rapid bolus and the KCl infusion was stopped. Hemodynamic measurements, blood-gas, and K⁺ determinations were obtained 1, 3, 5, 15, and 30 min after calcium administration.

Statistics were by Student's *t* test for paired and unpaired values as appropriate with *P* < 0.05 considered significant.

Results

During the study, PaCO₂ averaged 39 ± 1 mmHg (mean ± SE), PaO₂ 151 ± 4 mmHg, buffer base 39 ± 0 mEq/l, and end-tidal halothane 0.79 ± 0.01%.

Verapamil, studied 10 min after intravenous administration but prior to K⁺ infusion, did not result in significant changes in cardiac indexes (CI), MAP, PAWP, SVR, or HR (table 1). Group 1 (hyperkalemia alone) and Group 2 (verapamil plus hyperkalemia) were rendered acutely hyperkalemic to similar levels of serum K⁺ prior to Ca⁺⁺ therapy. (Group 1 K⁺ = 9.4 ± 0.2 mEq/l and Group 2 K⁺ = 8.2 ± 0.8 mEq/l).

Hyperkalemia in both Group 1 and Group 2 resulted in decreased CI compared with controls (Group 1 control CI = 4.2 ± 0.5 l \cdot min⁻¹ \cdot m⁻² decreased to 3.0 ± 0.2 l \cdot min⁻¹ \cdot m⁻² and Group 2 control CI = 3.7 ± 0.5 l \cdot min⁻¹ \cdot m⁻² decreased to 1.3 ± 0.5 l \cdot min⁻¹ \cdot m⁻²). The decrease in CI from control values during hyperkalemia was significantly greater in verapamil-pretreated dogs (Group 2 65% decrease in CI *vs.* Group 1 29% decrease in CI).

One minute after Ca⁺⁺ therapy, CI returned to control in Group 1 (control CI = 4.2 ± 0.5 l \cdot min⁻¹ \cdot m⁻² *vs.* 4.2 ± 0.4 l \cdot min⁻¹ \cdot m⁻² 1 min after Ca⁺⁺). In Group 2, CI was still significantly depressed 1 min after Ca⁺⁺ compared with control (Group 2 control CI = 3.7 ± 0.5 l \cdot min⁻¹ \cdot m⁻² *vs.* CI = 2.4 ± 0.4 l \cdot min⁻¹ \cdot m⁻² 1 min after calcium therapy). The difference in CI between Group 1 (4.2 ± 0.4 l \cdot min⁻¹ \cdot m⁻²) and Group 2 (2.4 ± 0.4 l \cdot min⁻¹ \cdot m⁻²) 1 min after Ca⁺⁺ is significant.

A decrease in MAP was seen only in the verapamil-

(Group 1—Hyperkalemia alone; Group 2—Verapamil and Hyperkalemia)

MAP (mmHg)		PAWP (mmHg)		CI ($l \cdot \text{min}^{-1} \cdot \text{m}^{-2}$)		SVRI ($\text{mmHg} \cdot l^{-1} \cdot \text{min} \cdot \text{m}^2$)		Number of Dogs with AV Block	
Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
97 ± 9	94 ± 13	2.0 ± 0.7	2.5 ± 1.2	4.2 ± 0.5	3.7 ± 0.5	24 ± 3	25 ± 5	0	0
—	85 ± 9	—	3.8 ± 1.1	—	4.1 ± 0.5	—	21 ± 2	—	0
96 ± 7	60 ± 13*	3.4 ± 0.8	5.0 ± 1.5	3.0 ± 0.2*†	1.3 ± 0.5*†	33 ± 4*	33 ± 7	3	3
110 ± 13	66 ± 7*	11.6 ± 5	4.7 ± 2.7	4.2 ± 0.4†	2.4 ± 0.4†	27 ± 6	26 ± 3	0†	5†
112 ± 12	93 ± 13	2.6 ± 0.5	4.5 ± 1.3	3.8 ± 0.3	2.8 ± 0.8	31 ± 6	43 ± 12	0	2

pretreated hyperkalemic animals (Group 2 control MAP = 94 ± 13 mmHg vs. 60 ± 13 mmHg prior to Ca⁺⁺ therapy and 66 ± 7 mmHg 1 min after Ca⁺⁺ therapy).

Heart rate was lower in the verapamil-pretreated animals with hyperkalemia 5 min after Ca⁺⁺ therapy (Group 2 HR = 86 ± 12 beats/min vs. Group 1 HR = 154 ± 16 beats/min).

Second degree A-V block was seen in three of five animals in both Groups 1 and 2 during hyperkalemia prior to Ca⁺⁺ therapy. Despite this, at 1 min after Ca⁺⁺ therapy, none of the Group 1 (without verapamil) animals continued to show second degree A-V block, whereas with verapamil pretreatment, all five animals with hyperkalemia showed persistent second degree block. One minute after Ca⁺⁺ therapy, the whole blood ionized calcium rose similarly in the hyperkalemic controls (2.9 ± 0.2 to 3.6 ± 0.2 mEq/l) and the verapamil pretreated animals (2.4 ± 0.1 to 3.3 ± 0.3 mEq/l). The Ca⁺⁺ rise in the verapamil pretreated group, though, did not reach statistical significance.

Despite identical infusion rates, the total mEq of KCl infused into the verapamil-pretreated dogs, which was required to produce similar ECG changes and which (in retrospect) resulted in similar serum potassium levels, was only one-third that required in dogs that were not pretreated with verapamil (Group 2 1.6 ± 0.3 mEq/kg KCl administered vs. Group 1 5.0 ± 0.7 mEq/kg KCl administered). The total K⁺ infusion time for verapamil pretreated dogs was 21 ± 5 minutes, while 66 ± 11 minutes was required to obtain a similar level of severe hyperkalemia in controls.

In three animals, urine output and urine K⁺ were measured. The urine output was much greater in animals not pretreated with verapamil (Group 1 253 ± 68 ml urine with 78 ± 18 mEq K⁺/ml) versus Group 2 (7 ± 6 ml urine with 118 ± 98 mEq K⁺/ml — K⁺ was not measured on one Group 2 animal).

One animal in Group 2 proceeded from second degree A-V block to ventricular fibrillation during severe hyperkalemia but was defibrillated successfully by DC cardioversion.

In addition to the five animals reported in this article, two other animals (one without and one with pretreatment) developed ventricular fibrillation intractable to DC cardioversion during the infusion of KCl before hemodynamics could be recorded prior to Ca⁺⁺ therapy.

Plasma concentrations of verapamil measured in Group 2 animals just prior to Ca⁺⁺ therapy averaged 130 ± 25 ng/ml (range: 64–190 ng/ml). No accumulation of nor-verapamil, the principle active metabolite of verapamil, was detected in these plasma specimens. The sensitivity limit of the procedure was 5 ng/ml.

Discussion

The findings that HR and SVRI in halothane-anesthetized dogs were not changed significantly 10 min after intravenous verapamil administration but prior to K⁺ infusion (table 1) are consistent with those of Kapur and Flacke.³ In dogs anesthetized with 1.1 MAC halothane and given a 0.2 mg/kg verapamil bolus, they reported no significant changes in HR, and early decreases in SVRI were back to control 10 min after verapamil administration. They reported a 12% decrease in MAP that is similar to the 10% (nonsignificant) decrease seen in our study. Flacke and Kapur³ reported an initial increase in CI 1 min after verapamil, a decrease in CI 10 min after verapamil, and a return to control CI for the remaining 60 min of their study. Our CI was not different from control 10 min after verapamil administration. They did not study hyperkalemic animals.

Mangiardi *et al.*² reported that at plasma verapamil concentrations of 92 ± 10 ng/ml, the drug had the desired antiarrhythmic effect, namely prolonging the atrio-his bundle conduction interval and abolishing ventriculoatrial conduction but that this concentration did not significantly decrease HR or cardiac output in thiopental-anesthetized dogs. Similar to the control findings of our study and the

report by Kapur and Flacke,³ Mangiardi *et al.*² reported a 12% decrease in MAP. They found that verapamil concentration below 152 ng/ml did not significantly alter HR, CO, left ventricular dp/dt, or SVR, but that concentrations above 200 ng/ml were associated with slowing of HR, high degree of A-V block during atrial pacing, a 24% decrease in MAP, and decreased CO and left ventricular dp/dt. The verapamil levels of 130 ± 25 ng/ml (all below 200 ng/ml) in our study during hyperkalemia therefore are considered to be in a hemodynamically safe therapeutic range for the dog. Failure to demonstrate accumulation of norverapamil is consistent with previous reports that intermittent intravenous administration of verapamil does not lead to accumulation of significant concentrations of this active metabolite.¹⁸

Surawicz *et al.*¹⁹ reported that hyperkalemia produced by infusion of KCl at a rate of $0.1 \text{ mEq} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ in barbiturate-anesthetized dogs did not result in decreases in CI or arterial pressure in plasma potassium ranges as high as 11.1 to 15.0 mEq/l. We also found no change in HR or MAP despite a serum K^+ of 9.4 ± 0.2 mEq in Group 1 animals (hyperkalemia alone), but in contrast to Surawicz *et al.*,¹⁹ we did observe a significant decrease in CI. The decrease in CI during acute hyperkalemia in our study possibly resulted from additive effects with the background anesthetic halothane, which is a potent direct myocardial depressant.⁴⁻⁶ The latter volatile agent as a background seems more clinically relevant than a purely barbiturate anesthetic.

When verapamil pretreatment was added to the combination of acute hyperkalemia and halothane anesthesia, which already had resulted in decreased CIs, it is not surprising that profound decreases in CI and markedly depressed MAP's resulted. In addition to halothane's myocardial depressant effects, a recent report has suggested that halothane itself may depress myocardial slow channel conductance.²⁰ The profound decreases in CI and MAP seen in the verapamil-pretreated group probably resulted from the addition of the known myocardial depressant and direct peripheral vasodilatory effects of verapamil to the hyperkalemic and volatile anesthetic effects. This or similar combinations of direct myocardial depressant, adrenergic blockade, and peripheral vasodilatory effects are not theoretic at all in today's medically treated patients with coronary artery disease who are scheduled to undergo anesthesia and surgery.

Hyperkalemia in the dog resulted in second degree A-V block in 76 of 78 consecutive infusions of K^+ reported by Fisch *et al.*¹⁰ In humans, second and third degree A-V block due to hyperkalemia is considered to be unusual in noniatrogenic (*i.e.*, more chronic) hyperkalemia, with intraventricular conduction defects reported more commonly.^{11,21,22} This is in contrast to a report of administration of large oral doses of potassium²³ and more recent case reports by Cohen *et al.*²²

Calcium is considered to be initial therapy of choice for acute hyperkalemia.^{12,13,15} When the resting membrane is depolarized partially by the presence of hyperkalemia, it is thought that increasing the extracellular calcium concentration brings the threshold potential also closer to zero, thus restoring previous membrane excitability albeit at less overall negative potential.¹² In our model, Ca^{++} restored CI to control and eliminated second degree A-V block in hyperkalemic halothane-anesthetized animals without verapamil (Group 1). By contrast, Ca^{++} treatment in the presence of the above, plus the slow calcium channel blocker verapamil, only partially corrected the more severely depressed CI and had no beneficial effect on the second degree A-V block. In fact, all dogs in the verapamil-pretreated Group 2 had persistent second degree A-V block 1 min after Ca^{++} therapy, whereas none of the Group 1 animals had second degree A-V block after Ca^{++} . The findings that Ca^{++} therapy for hyperkalemia in the presence of calcium entry blockers partially reversed the hemodynamic depression but not the A-V block is consistent with the finding by Hariman *et al.*,²⁴ that increasing serum Ca^{++} by 40% comparable to the increase in whole blood ionized Ca^{++} seen in our experiment would reverse the hemodynamic depression of verapamil but not the effects of verapamil on A-V conduction, at least in normokalemic animals. High concentrations of halothane itself also are reported to decrease conduction through the A-V node.⁹ Verapamil did not appear to alter whole blood free ionized Ca^{++} during hyperkalemia or the rise in whole blood Ca^{++} after calcium therapy.

Potassium was infused into Group 1 and Group 2 dogs at the same rate to an ECG endpoint indicative of severe hyperkalemia. Near-identical peak serum K^+ levels resulted. Despite this, we were surprised to find that the time and therefore the total amount of KCl infused into Group 2 dogs was explained only partially by the higher urine volume in the dogs not pretreated with verapamil (Group 1). The net potassium infused in the three Group 1 dogs in which urine was collected was 44 mEq (63 mEq less 19 mEq excreted in the urine) compared with 16 mEq (17 mEq less 1 mEq excreted) in the three Group 2 dogs. Therefore, despite correcting for urinary excretion, almost three times as much *net* K^+ was infused into Group 1 animals *versus* Group 2 in order to obtain similar ECG endpoints and serum K^+ levels (determined minutes later). Decreased urine production in the verapamil-hyperkalemic group probably was prerenal in origin because of decreased MAP and CI. A possible explanation for verapamil's apparent decreasing of K^+ tolerance is that verapamil may decrease net inward flux of excess K^+ into cells. Plasma, interstitial, and lymph K^+ are only 1.5-2% of total body K^+ (≈ 48 mEq compared with ≈ 3600 mEq intracellularly).²⁵ A major protective mechanism against hyperkalemia is movement of K^+ into the large intra-

cellular pool.^{10,12,25} At least in cardiac Purkinje fibers, the Ca^{++} entry blockers have been shown to increase the net outward time-independent plateau current, which is largely carried by potassium ions.²⁶ During hyperkalemia, calcium channel blockers similarly may decrease the net movement of excess extracellular K^+ intracellularly. Clearly, in our experiments, verapamil rendered the homeostatic mechanisms against development of acute serum hyperkalemia considerably (circa three times) less effective.

We conclude the following: 1) verapamil renders hyperkalemia likely after considerably less K^+ administration; 2) the hemodynamic depression seen during hyperkalemia in halothane-anesthetized dogs is much more severe in the presence of verapamil (plasma levels 130 ± 25 ng/ml); 3) calcium therapy (a 36% increase in whole blood ionized Ca^{++}) is only partially effective in reversing the hemodynamic depression caused by hyperkalemia in the presence of the Ca^{++} entry blocker verapamil; 4) Ca^{++} in the dosage studied is not therapeutic for second degree A-V block seen in the hyperkalemic dog pretreated with verapamil, with halothane as anesthesia.

Considering the limitation that our results were obtained in a canine model and not a human, the potential clinical significances of our findings are as follows. First, severe hyperkalemia in the patient treated with verapamil may occur after much smaller quantities of intravenous KCl and/or fewer transfusions of near-outdated blood. Verapamil also might be expected to markedly inhibit potassium tolerance in patients with chronic renal failure and inability to excrete dietary K^+ . Second, in the verapamil-pretreated patient, more severe hemodynamic depression due to hyperkalemia will likely occur than would be expected from hyperkalemia alone. Finally, in the presence of the calcium entry blocker verapamil, although calcium therapy may improve (but not totally reverse) depressed hemodynamics due to acute hyperkalemia, it may not improve cardiac conduction defects, at least in the presence of halothane anesthesia.

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