Anesthesiology
66:246–249, 1987

Hyperkalemia, Verapamil, and Dantrolene

ALEXANDER S. RUBIN, M.D.,* ALAN D. ZABLOCKI, M.D.†

The concurrent administration of verapamil and parenteral dantrolene has resulted in hyperkalemia and cardiovascular collapse in animals.[1–3] This possible drug interaction has not been described in humans. We describe the anesthetic experiences of a malignant hyperthermia (MH) susceptible patient with coronary artery disease (CAD) being treated with verapamil who developed hyperkalemia and myocardial depression following parenteral dantrolene. Hyperkalemia and myocardial depression did not occur following parenteral dantrolene when nifedipine was substituted for verapamil for a subsequent operation in the same patient.

REPORT OF TWO CASES

Case 1. A 92-kg, 60-yr-old man with cancer of the colon was scheduled for a right hemicolectomy. In 1968 he survived an MH crisis with a peak temperature exceeding 43° C during a staging laparotomy for lymphocytic lymphoma. No other information about the event was available, and no muscle biopsy has been performed. Family history is significant for two grandchildren who developed rigidity upon induction of general anesthesia. Since then, he has had several surgical procedures for which prophylactic dantrolene was given orally without complications. In 1985, he underwent a cardiac catheterization for increasing angina, which demonstrated diffuse, inoperable two-vessel disease involving the left anterior descending and right coronary arteries, an ejection fraction of 50%, and the absence of wall motion abnormalities. Verapamil 80 mg was given three times daily, and he has had no angina since. A review of systems revealed insulin-dependent diabetes mellitus and lymphocytic lymphoma (in remission). His medications were insulin, 20 units NPH and 20 units regular every morning, Transderm®-Nitro 10 mg daily, and verapamil 80 mg three times daily. He denied smoking or use of caffeine or alcohol. Review of systems was otherwise negative. Physical examination was unremarkable, and preoperative laboratory results were all within normal limits, with a serum potassium of 4.6 mmol/l and serum glucose of 92 mg/dl. The preoperative ECG demonstrated normal sinus rhythm with nonspecific ST–T wave changes. The patient expressed severe anxiety regarding the forthcoming surgery and therefore was given oral diazepam 10 mg three times daily for 5 days prior to surgery.

In preparation for the surgery, an anesthesia machine was purged with oxygen for 24 h prior to surgery, all rubber parts and CO_2 absorbent were changed, and the vaporizers were drained and left open. An infusion of 5% dextrose in 0.9% saline was started on the night before surgery at 75 ml/h. Ranitidine 150 mg at bedtime followed by oral ranitidine 150 mg, metoclopramide 10 mg, diazepam 15 mg, verapamil 80 mg, im morphine 10 mg, and Transderm®-Nitro 10 mg were given 1 h prior to arrival in the operating room. The morning dose of insulin was withheld. When the patient arrived in the operating room drowsy, ECG (leads V_5 and II) and arterial blood pressure monitoring were instituted. A second iv and a radial arterial line were inserted. The right internal jugular vein was cannulated and a pulmonary artery (PA) catheter was inserted. Arterial blood pressure, heart rate, mixed venous oxygen saturation (Sv_{O_2}), end-tidal CO_2 (PET_{CO_2}), temperature (central core *via* pulmonary artery catheter and nasopharyngeal *via* flexible temperature probe), inspired oxygen concentration (FI_{O_2}), urine output, and neuromuscular blockade were monitored continuously. Cardiovascular parameters (cardiac output [CO], pulmonary artery diastolic pressure [PAD], pulmonary artery wedge pressure [PAWP]) were measured every 15 min, and arterial blood samples (Pa_{O_2}, Pa_{CO_2}, pH_a, base excess [BE], bicarbonate, total Ca, K^+, glucose, and creatinine phosphokinase [CPK]) were drawn hourly for 6 h, then every 2 h for 24 h, then every 4 h for 24 h.

Two hours after oral verapamil was given, arterial and venous blood was drawn; a set of hemodynamic measurements were obtained; and dantrolene (2.4 mg/kg, total dose 220 mg) was infused iv over 30 min. The patient tolerated the infusion well but did report feeling of "weakness." Following completion of the dantrolene infusion, anesthesia was induced with an iv 33 μg/kg bolus of fentanyl and atracurium 50 mg. Ventilation was controlled with 100% oxygen, and no other anesthetic agents or additional muscle relaxant were given during the 1-h procedure. Normothermia was maintained with a warming blanket, humidifier, and by warming all iv fluids. During the intraoperative period, CO and PAD/PAWP did not change significantly from a baseline of 4.5 l/min (cardiac index [CI] of 2.1) and 14/13 mmHg, respectively. PET_{CO_2} and mixed venous oxygen saturation remained stable at 34–36 mmHg and 70–72%, respectively. Estimated blood loss was 250 ml, and iv fluid replacement consisted of 1 l of lactated Ringer's solution, 1 l of 5% dextrose in lactated Ringer's solution, and 500 ml of 5% hetastarch. Urine output averaged 1.5 $ml \cdot kg^{-1} \cdot h^{-1}$. At the conclusion of surgery, four out of four twitches were observed, but the patient made no spontaneous respiratory effort. Narcotic reversal with naloxone was not considered because of the possibility of undesirable cardiovascular stimulation, therefore the trachea remained intubated. In the intensive care unit (ICU), the patient was mechanically ventilated in the intermittent mandatory ventilation (IMV) mode. Intensive monitoring with ECG, BP, PAP,CO, Sv_{O_2}, PET_{CO_2}, and central core temperature *via* PA catheter was continued in the ICU. Sedation and analgesia were accomplished with incremental iv doses of morphine sulfate.

Blood chemistries were drawn at the indicated times, but the results were not available for 1–1.5 h. Immediately prior to the dantrolene

* Anesthesiology Resident. Current Position: Chief, Anesthesia and Operative Service, Gen. Leonard Wood Army Hospital, Ft. Leonard Wood, Missouri.

† Staff Anesthesiologist. Current Position: Assistant Professor of Anesthesiology, University of Texas Health Science Center at San Antonio, San Antonio, Texas.

Received from the Department of Surgery, Anesthesia and Operative Service, Brooke Army Medical Center, Fort Sam Houston, Texas. Accepted for publication September 15, 1986.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

Address reprint requests to Dr. Rubin: 41 Delafield Drive, Ft. Leonard Wood, Missouri 65473.

Key words: Complications: hyperkalemia. Hyperthermia: dantrolene. Pharmacology: verapamil, nifedipine.

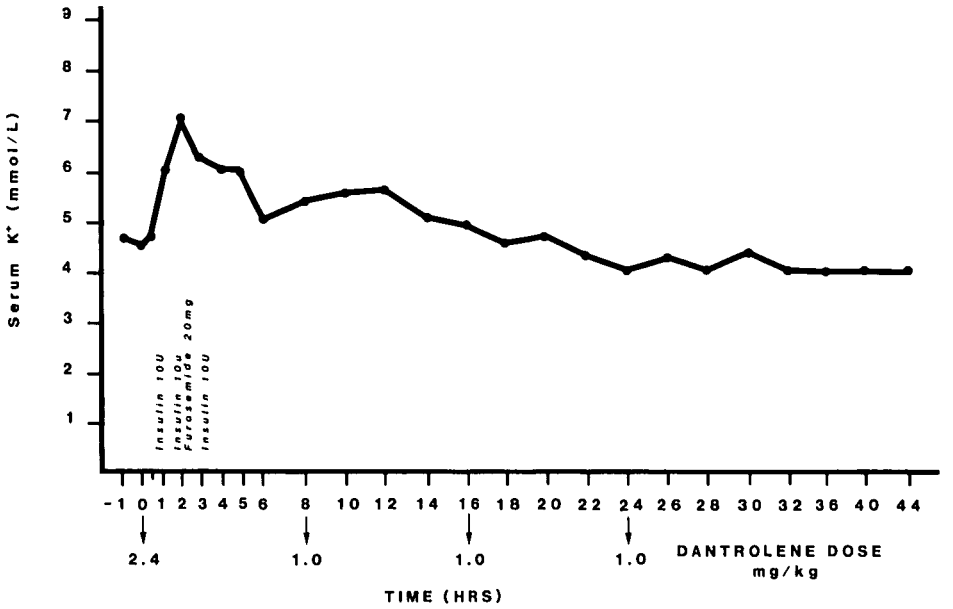

FIG. 1. Serum K^+ concentration *vs* time of dantrolene administration and therapeutic interventions.

infusion, serum glucose was 152 mg/dl and the serum K^+ was 4.7 mmol/l. Immediately postinfusion, serum glucose was 210 mg/dl, and the K^+ was 4.6 mmol/l. The K^+ and serum glucose drawn 1.5 h post dantrolene infusion (near the conclusion of surgery) were 6.1 mmol/l and 280 mg/dl, respectively (see fig. 1). The patient had been in the ICU for 30 min when these results became available. Ten units of iv regular insulin were given. Two and one-half hours post dantrolene infusion (45 min after the completion of the surgery), the K^+ was 7.1 mmol/l and serum glucose was 351 mg/dl. Regular insulin 10 units iv and furosemide 20 mg iv were given. At 3.5 h post infusion, the K^+ had fallen to 6.3 mmol/l, and serum glucose was 278 mg/dl. Another 10 units of regular insulin was given iv. At 4.5 h post dantrolene infusion, when K^+ was 6.0 mmol/l and serum glucose was 255 mg/dl, the CO decreased to 3.0 l/min (CI of 1.4), and a metabolic acidosis (pH_a 7.3, Pa_{O_2} 179 mmHg, Pa_{CO_2} 23 mmHg, BE −12.6 mmol/l, bicarbonate 11.4 mmol/l) ensued. No evidence of hypermetabolism or myocardial ischemia was found (temperature = 35.9° C, HR = 68 beats/min, BP = 116/80 mmHg, PAD/PAWP = 11/10 mmHg). Hetastarch 5%, 500 ml, and 150 mEq of HCO_3^- were rapidly infused iv. The PAD/PAWP increased to 14/13 mmHg with improvement of the CO to 4.0 l/min (CI of 1.9), and resolution of the metabolic acidosis (pH_a 7.47, BE 6.8 mmol/l, bicarbonate 29.9 mmol/l). The patient experienced no further cardiovascular depression, and the trachea was extubated 11 h after arrival in the ICU. He received three additional doses of dantrolene (1 mg/kg iv every 8 h) but did not develop either hyperkalemia or decreased CO. Hyperglycemia exceeding 250 mg/dl was treated with iv insulin. Methyldopa 250 mg iv every 6 h was started for postoperative hypertension. No ischemic or hyperkalemic ECG changes or evidence of impaired atrioventricular (AV) conduction as manifested by an increase in P–R interval were observed at any time during the perioperative period. The patient denied any anginal episodes or intraoperative recall. Total serum calcium remained within normal limits, and CPK remained below 200 μ/l. Verapamil was restarted 48 h post surgery. The patient was discharged on the 10th postoperative day.

Case 2. Six months later, the same patient required extensive oral surgery. The patient's condition was unchanged, and similar preoperative and intraoperative approaches were chosen. However, 2 weeks prior to surgery, verapamil was discontinued, and the patient was begun on nifedipine, 10 mg three times daily. He remained angina-free. Preoperative serum K^+ was 4.1 mmol/l. On the morning of surgery, the patient was given his usual dose of nifedipine, and, 2 h later, dantrolene was administered (2.4 mg/kg iv). Anesthesia was induced with a 50 μg iv bolus of sufentanil and maintained with a sufentanil infusion at 0.1–0.2 $\mu \cdot kg^{-1} \cdot h^{-1}$ and controlled ventilation with 50%/50% N_2O/O_2. Muscle relaxation was achieved with atracurium iv (60 mg total dose). The 75-min operation was uneventful. By the end of the surgery, the patient had complete recovery of neuromuscular function manifested by four-of-four twitches and sustained tetany at 100 Hz, and no reversal agents were given. Since he was awake and responsive without evidence of respiratory depression, his trachea was extubated in the operating room.

The serum K^+ increased to a peak of 5.4 mmol/l in the postoperative period (3 h after dantrolene infusion and 5 h after nifedipine) and gradually returned to the preoperative level over the next 3 h without treatment. No evidence of malignant hyperthermia, myocardial ischemia or depression, dysrhythmias, or acidosis were noted at any time in the perioperative period. No additional dantrolene was administered, and nifedipine was restarted 8 h post surgery. The patient was discharged on the 3rd postoperative day.

DISCUSSION

Management of an MH-susceptible patient with CAD has not been previously described to our knowledge. A perioperative MH crisis could be especially disastrous in a patient with CAD because the hypermetabolic state and associated sympathetic discharge could precipitate myocardial ischemia and/or infarction.

The development of hyperkalemia within 2 h following dantrolene administration in healthy humans has been described.[4] Hyperkalemia and cardiovascular collapse in verapamil- or diltiazem-pretreated swine that subsequently received iv dantrolene have been reported.[2,5] These changes were not observed with nifedipine pre-

treatment.[5] Similar results were seen in verapamil-pretreated dogs.[1,3] Depression of cardiac contractility and AV conduction caused by this drug interaction has also been described.[6,7] Elevated serum K^+ levels augment the negative dromotropic and inotropic effects of verapamil, which renders the homeostatic mechanisms that protect against hyperkalemia much less effective.[8] Saltzman *et al.*[2] postulated that compensatory mechanisms for a dantrolene-induced increase in serum K^+ might be limited in the presence of verapamil, and that any decrease in the CO also caused by this drug combination would further impair potassium homeostasis by decreasing perfusion to tissues that are involved in the uptake and excretion of K^+, such as the liver, skeletal muscles, and kidneys. Nifedipine has minimal negative inotropic and dromotropic properties *in vivo*,[9] which might account for the lack of similar changes when it is combined with dantrolene.

We observed hyperkalemia and myocardial depression in our patient who received iv dantrolene following oral verapamil. An initial rise of serum K^+ to 6.1 mmol/l was noted 1.5 h post iv dantrolene, and reached a peak of 7.1 mmol/l 2.5 h post dantrolene and 5 h post verapamil, which corresponds with maximum blood levels of oral verapamil[10] and iv dantrolene.[11] No other readily identifiable cause for either event was found in this patient. No evidence of myocardial ischemia, hypermetabolism, or hypovolemia was observed. Although ketone bodies were not measured, diabetic ketoacidosis was thought to be unlikely because acidosis occurred 3 h after the hyperglycemia was treated with insulin, and the blood glucose levels were on the decline. Verapamil was then withheld until 24 h following the last dantrolene dose, and no further episodes of hyperkalemia or cardiovascular depression were observed. Although a rise in serum K^+ did occur, significant hyperkalemia and myocardial depression were not observed when nifedipine was substituted for verapamil in case two. The mild increase in serum K^+ that occurred following the second operation could be explained by the dantrolene alone[4] or possibly by an interaction between dantrolene and nifedipine similar to that with verapamil but of much lesser magnitude.

We were aware of the aforementioned animal data and were concerned about the possibility of drug interactions, but we elected to administer oral verapamil and iv dantrolene to our patient prior to case one and to monitor for hyperkalemia and cardiovascular depression. Although a muscle biopsy has not been performed, the diagnosis of MH susceptibility was not questioned in our patient in light of his clinical history. We felt that dantrolene prophylaxis was absolutely necessary because of the patient's high anxiety level and the nature of surgery,[12] as well as our concern that even the earliest stages of hypermetabolism associated with an MH crisis could result in myocardial ischemia or infarction. Verapamil was continued because of dramatic improvement of the patient's angina following the initiation of treatment with this drug. We felt that the potential risk of discontinuing verapamil (precipitation of myocardial ischemia[10]) outweighed the potential risks of interaction with dantrolene. The dose, route of administration, timing, and purpose of verapamil were different in our patient with CAD compared with the animal studies.

Hyperkalemia and decreased CO following verapamil and dantrolene administration in our patient are consistent with previous observations in animals. If an MH-susceptible patient with CAD on verapamil or diltiazem requires dantrolene prophylaxis, extreme caution should be used. Consideration should be given to changing to nifedipine, because adverse effects have not been observed in swine when this drug was combined with dantrolene.[5] We had the opportunity to allow the patient to serve as his own control to some degree during case two, and our observations were consistent with the animal data cited earlier. Alternative management might include a smaller loading dose of dantrolene or withholding dantrolene entirely unless the patient exhibits evidence of hypermetabolism. However, perioperative MH episodes have been reported in patients who received "safe" anesthetics but did not receive parenteral dantrolene prophylaxis.[13] Patients with CAD may not have the margin of safety necessary to tolerate the early hypermetabolic state of an MH crisis prior to treatment. Whenever calcium entry blockers, especially verapamil or diltiazem, and dantrolene must be administered concurrently, invasive hemodynamic monitoring and frequent measurement of serum K^+ levels are recommended.

References

1. Lynch C, Durbin CG, Fisher NA, Veselis RA, Althaus JS: Effects of dantrolene and verapamil on atrioventricular conduction and cardiovascular performance in dogs. Anesth Analg 65:252–258, 1986
2. Saltzman LS, Kates RA, Corke BC, Norfleet EA, Heath KR: Hyperkalemia and cardiovascular collapse after verapamil and dantrolene administration in swine. Anesth Analg 63:473–478, 1984
3. San Juan AC, Port JD, Wong KC: Hyperkalemia after dantrolene administration in dogs (abstract). Anesth Analg 65:S131, 1986
4. Collier CB: Dantrolene and suxamethonium. Anaesthesia 34:152–158, 1979
5. Saltzman LS, Kates RA, Norfleet EA, Corke BC, Heath KS: Hemodynamic interactions of diltiazem–dantrolene and nifedipine–dantrolene (abstract). ANESTHESIOLOGY 61:A11, 1984
6. Roewer N, Rumberger E, Schulte am Esch J: Effects of dantrolene on excitation–contraction coupling in isolated heart muscle (abstract). ANESTHESIOLOGY 61:A255, 1984
7. Roewer N, Rumberger E, Bode H, Schulte am Esch J: Electrophysiological and mechanical interactions of verapamil and dantrolene on isolated heart muscle (abstract). ANESTHESIOLOGY 63:A274, 1985
8. Nugent M, Tinker JH, Moyer TP: Verapamil worsens rate of development and hemodynamic effects of acute hyperkalemia

on halothane-anesthetized dogs: Effects of calcium therapy. ANESTHESIOLOGY 60:435–439, 1984
9. Henry PD: Comparative pharmacology of calcium antagonists: Nifedipine, verapamil and diltiazem. Am J Cardiol 46:1047–1058, 1980
10. McGoon MD, Vlietstra RE, Holmes DR, Osborn JE: The clinical use of verapamil. Mayo Clin Proc 57:495–510, 1982
11. Flewellen EH, Nelson TE, Jones WP, Arens JF, Wagner DL: Dantrolene dose response in awake man: Implications for management of malignant hyperthermia. ANESTHESIOLOGY 59:275–280, 1983
12. Britt BA: Malignant hyperthermia. Can Anaesth Soc J 32:6:667–677, 1985
13. Grinberg R, Edelist G, Gordon A: Postoperative malignant hyperthermia episodes in patients who received "safe" anaesthetics. Can Anaesth Soc J 30:3:273–276, 1983

Anesthesiology
66:249–252, 1987

Inhibition of Postanesthestic Shivering with Radiant Heat

A. SHARKEY, M.B., B.CH., B.A.O., F.F.A.R.C.S.,* J. M. LIPTON, PH.D.,†
M. T. MURPHY, M.D.,‡ A. H. GIESECKE, M.D.§

Postanesthetic shivering (PAS) with its attendant subjective feeling of intense cold is one of the most distressing aspects of the immediate postoperative period for many patients. PAS is associated with an increase in oxygen consumption[1]; it generally adds an extra burden to the cardiopulmonary system, which may already be compromised in some patients. Indeed, myocardial infarction[2] has been linked with the marked increase in oxygen demand and the hypoxemia that occurs with PAS.[3–5] Although there is general agreement that PAS should be prevented, many contributing factors, such as low ambient temperature in the operating room, use of cold fluids for infusion, *etc.*[6,7,**] are not easy to control. Certain drugs such as methylphenidate[8] and opiates[9] have been used to stop PAS with only partial success, and injections of the amino acid taurine have inhibited PAS in monkeys,[10] but administration of additional drugs in the postoperative period may not be the best solution. In recent studies of PAS in an unoperated, anesthetized, subhuman primate model,[10] acute application of radiant heat to the skin immediately interrupted shivering even though deep body temperature remained low. Rapid changes in shivering as the heat lamp was turned on and off suggested that a similar technique might be useful in the control of PAS in humans. This effect was tested on PAS in obstetric patients in studies described in the following. Positive findings in these experiments led us to compare the effect on duration of PAS of constant radiant heat exposure with PAS duration when warm blankets were used.

METHODS

Experiment 1: Acute, Repeated Applications of Radiant Heat

Subjects: After the entire study protocol was approved by the Institutional Review Board, 30 female obstetric patients classified as ASA I or II who shivered postoperatively were studied. These patients had either a cesarean section or postpartum tubal ligation performed under general, spinal, or epidural anesthesia. Their average age was 25.2 ± 1.1 (SEM) yr, and their average weight was 74.1 ± 3.3 (SEM) kg. All patients were tested in the postoperative recovery area immediately after surgery.

Anesthetic procedures: Sodium citrate (15 ml, po) was given to the cesarean section patients, and diazepam (10 mg, po) was additionally given to the patients having tubal ligations, as preoperative medications.

Thiopental sodium (4 mg/kg) was used for induction of general anesthesia, and succinylcholine (1–1.5 mg/kg) and atracurium (0.3–0.5 mg/kg) were given for muscle relaxation. All patients received N_2O and O_2 in a concentration of 70/30% except when administered prior to delivery when a 50/50% concentration was used. Isoflurane (22 cases) and enflurane (8 cases) were added to the basal anesthetic. Fentanyl (2–3 μg/kg, iv) and droperidol (2.5 mg iv) were given after clamping the cord in those patients having a cesarean section and at induction in all others. All of those having cesarean section received morphine 5 mg iv shortly before the end of the procedure.

The patients receiving spinal anesthesia were given 5% lidocaine in 10% dextrose (average dose 70 mg). For epi-

---

* Visiting Fellow.

† Professor of Physiology, Assistant Professor of Anesthesiology.

‡ Medical Student IV.

§ Professor of Anesthesiology and Chairman, Department of Anesthesiology.

Received from the Departments of Anesthesiology and Physiology, Southwestern Medical School, University of Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas Texas 75235. Accepted for publication September 5, 1986.

Address reprint requests to Dr. Lipton.

Key words: Complications: shivering. Hypothermia: postoperative; radiant heat; shivering. Temperature: monitoring; regulation.

** Flacke JW, Flacke WE: Inadvertent hypothermia: Frequent, insidious and often serious. Seminars in Anesthesia 2:183–196, 1983.