Hyperkalemia, Verapamil, and Dantrolene

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The concurrent administration of verapamil and parenteral dantrolene has resulted in hyperkalemia and cardiovascular collapse in animals.1-5 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 1986 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 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 CO₂ 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, ECG leads V₁ 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 (SVO₂), end-tidal CO₂ (PETCO₂), temperature (central core via pulmonary artery catheter and nasopharyngeal via flexible temperature probe), inspired oxygen concentration (FiO₂), 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 (PaO₂, PaCO₂, pH, 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 not report feeling of "weakness." Following completion of the dantrolene infusion, anesthesia was induced with an iv 50 mg 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. PETCO₂ and mixed venous oxygen saturation remained stable at 34–56 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·kg⁻¹·h⁻¹. At the conclusion of surgery, four 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/C0₂, SVO₂, PETCO₂, 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
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 hours postdantrolene 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 minutes when these results became available. Ten units of iv regular insulin were given. Two and one-half hours post dantrolene infusion (45 minutes 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 hours 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 hours post dantrolene infusion, when K⁺ was 6.0 mmol/l and serum glucose was 255 mg/dl, the CO decreased to 3.0 1/min (CI of 1.4), and a metabolic acidosis (pH 7.5, PaO₂ 179 mmHg, PaCO₂ 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 = 106/80 mmHg, PAd/PAPW = 79/70 mmHg). Heptastarch 5%, 500 ml, and 150 mEq of HCO₃⁻ were rapidly infused iv. The PAd/PAPW increased to 14/13 mmHg with improvement of the CO to 4.0 1/min (CI of 1.9), and resolution of the metabolic acidosis (pH 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 hours after arrival in the ICU. He received three additional doses of dantrolene (1 mg/kg iv every 8 hours) 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 hours 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 u/l. Verapamil was restarted 48 hours 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 peroperative 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 hours later, dantrolene was administered (2.4 mg/kg iv). Anesthesia was induced with a 50-µg bolus of sufentanil and maintained with a sufentanil infusion at 0.1-0.2 µg·kg⁻¹·h⁻¹ and controlled ventilation with 50%/50% N₂O/O₂. 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 hours after dantrolene infusion and 5 hours after nifedipine) and gradually returned to the preoperative level over the next 3 hours 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 hours 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 hours following dantrolene administration in healthy humans has been described. Hyperkalemia and cardiovascular collapse in verapamil- or diltiazem-pretreated swine that subsequently received iv dantrolene have been reported. These changes were not observed with nifedipine pre-
treatment. Similar results were seen in verapamil-pre-
treated dogs. Depression of cardiac contractility and
AV conduction caused by this drug interaction has also
been described. 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. Saltzman et al. postulated that compensatory mechanisms for a dantro-
lene-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. Ni-
fedipine has minimal negative inotropic and dromotropic properties in vivo, 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 correspond with maximum blood levels of oral
verapamil and iv dantrolene. No other readily identi-
tifiable 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 hy-
perglycemia was treated with insulin, and the blood glu-
cose levels were on the decline. Verapamil was then with-
held 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 sub-
stituted for verapamil in case two. The mild increase in
serum K⁺ that occurred following the second operation
could be explained by the dantrolene alone or possibly
by an interaction between dantrolene and nifedipine simi-
lar 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 dan-
trolene to our patient prior to case one and to monitor
for hyperkalemia and cardiovascular depression. Al-
though 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 dantro-
lene prophylaxis was absolutely necessary because of the
patient’s high anxiety level and the nature of surgery, as
well as our concern that even the earliest stages of hy-
permetabolism associated with an MH crisis could result
in myocardial ischemia or infarction. Verapamil was con-
tinued 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) 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 consist-
tent with previous observations in animals. If an MH-sus-
sceptible patient with CAD on verapamil or diltiazem re-
quires 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.
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 en-
tirely unless the patient exhibits evidence of hypermeta-
bolism. However, periooperative MH episodes have been
reported in patients who received “safe” anesthetics but
did not receive parenteral dantrolene prophylaxis. Patients
with CAD may not have the margin of safety neces-
sary 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 hemody-
amic monitoring and frequent measurement of serum K⁺
levels are recommended.

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Inhibition of Postanesthetic Shivering with Radiant Heat

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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; it generally adds an extra burden to the cardiopulmonary system, which may already be compromised in some patients. Indeed, myocardial infarction has been linked with the marked increase in oxygen demand and the hypoxemia that occurs with PAS. 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., are not easy to control. Certain drugs such as methylphenidate and opiates have been used to stop PAS with only partial success, and injections of the amino acid taurine have inhibited PAS in monkeys, but administration of additional drugs in the postoperative period may not be the best solution. In recent studies PAS in an unoperated, anesthetized, subhuman primate model, 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 N₂O and O₂ 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-