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0022-5282/90/3003-0353$02.00/0
THE JOURNAL OF TRAUMA
Vol. 30, No. 3
Printed in U.S.A.
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Fatal Iodine Toxicity following Surgical Debridement of a Hip Wound: Case Report

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This report presents the case of a patient who expired 10 hours following and emergent hip-wound debridement where Betadine™, a povidone iodine solution, was used to provide continuous postoperative wound irrigation. Toxic manifestations of systemic iodine absorption appeared to cause her demise.

Povidone iodine solution (P.I.S.) is extensively used intra- and postoperatively as a wound irrigant to promote antisepsis. Although P.I.S. is regarded as having little systemic toxicity, we encountered a patient who expired 10 hours following an emergent hip-wound debridement where Betadine™, a P.I.S. preparation, was used to provide continuous postoperative wound irrigation. The serum total iodine level at necropsy was 7,000 μg per 100 ml (normal value, 5–8 μg 100 ml). This extraordinarily high serum iodine concentration can produce refractory high anion gap metabolic acidosis, cardiogenic shock, and death (1–3).

CASE REPORT

A 74-year-old black woman presented to the Brigham and Women's Hospital emergency ward with a 4-day history of migratory knee and hand arthralgias culminating in incapacitating left hip pain. Past medical history was remarkable for hypothyroidism, Type II diabetes mellitus, essential hypertension, and hypochromic, microcytic anemia. Medications included Synthroid™, 0.15 mg *qd*, Diabenese™, 250 mg *qd*, hydrochlorothiazide, 100 mg *qd*, and oral potassium supplements. She reported no previous operations, and denied allergies or alcohol and tobacco consumption.

On physical examination, she was a 167-cm, 72-kg woman in obvious distress upon passive manipulation of the left hip joint. BP was 120/70 mm Hg, pulse 80/min and regular, with an oral temperature of 101.8°C. Auscultation of the chest revealed scattered rhonchi without wheezes or dullness. The remainder of the physical examination was unremarkable. She was clinically euthyroid.

Laboratory findings included a hematocrit of 31.4% with hypochromic, microcytic indices, WBC 14,800, and differential count with 83% polymorphonuclear leukocytes, 14% lymphocytes, and 3% monocytes. Her erythrocyte sedimentation rate was elevated at 110 mm in 1 hour with a normal coagulation profile. Serum electrolytes were: Na^+ = 134 mEq per liter, 100 ml, K^+ = 3.2 mEq per liter, Cl^- = 97 mEq per liter, and HCO_3 = 29 mEq per liter. A random serum glucose was 179 mg per 100 ml, BUN 26 mg/100 ml, and creatinine 1.4 mg/100 ml. Urinalysis revealed a trace positive glucose with negative ketones. Serum uric acid was elevated at 9.7 mg/100 ml. Calcium, phosphorus, and total protein values were normal. Thyroid function tests on replacement L-thyroxine therapy were T4 = 8.1 (5–10.2) and TBG = 1.05 (0.85–1.10).

X-ray films of the chest showed clear lung fields with borderline cardiomegaly and a hiatus hernia. An electrocardiogram revealed normal sinus rhythm at the rate of 80/min with left bundle-branch block, new since the last ECG 3 years earlier.

Needle aspiration of the left hip performed in the emergency ward yielded 4 ml of frank pus with possible intracellular Gram-positive diplococci seen on Gram stain. Intravenous antibiotics were administered following bacterial cultures of urine, hip aspirate, and blood. The patient then underwent emergency incision and drainage of a septic left hip after correction of her serum potassium deficit (40 mEq K^+ infused over 1 hour).

Induction of general endotracheal anesthesia with 60% nitrous oxide and enflurane proceeded smoothly. The intraoperative course and emergence from anesthesia were uneventful, inconsistent with clinical hypothyroidism (4, 5). No blood was administered during the procedure.

Upon transfer of the patient to the recovery room, a povidone antiseptic regimen was begun, consisting of intravenous antibiotics supplemented by continuous irrigation of her hip wound with a one-quarter strength solution connected to Hemovac™ drainage. Six hours postoperatively, the patient began to produce moderate amounts of nonpurulent sputum. The oral temperature was 99.0°F. Eight hours postoperatively, she vomited approximately 50 ml of bilious fluid. At this time, oral temperature had risen to 100°F and she was found to be mildly tachypneic, with a respiratory rate of 26 per minute. Vital signs remained stable. Bladder catheterization yielded 500 ml of dark-yellow urine.

Ten hours postoperatively, the patient was found unresponsive and pulseless with agonal respirations. Cardiopulmonary resuscitation was begun and ECG monitoring revealed a junctional rhythm at 75/min. Systolic blood pressure was palpable at 90–120 mm Hg, and spontaneous respirations had resumed. Bibasilar rales were present in both lungs. There was no evidence of periorbital edema, macroglossia, urticaria, or other signs of an anaphylactoid reaction. An arterial blood gas sample revealed pH = 7.18, PCO_2 = 43 mm Hg, and PO_2 = 227 mm Hg on 100% inspired oxygen via endotracheal tube. Base excess was −12 mmol/L, indicative of a high anion gap. The serum potassium was 4.9 mEq per liter. The serum glucose was 510

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mg/100 ml following intravenous administration of 50 ml of 50% glucose and 10 units of CZI-insulin. Serum SGOT was 639 IU/ml, LDH 1,380, and CPK 2,260 IU/ml. It was noted that approximately 800 ml of the povidone irrigating solution (containing 0.25% available iodine) had been infused at the left hip site. Hemovac™ drainage was only 100 ml. Wound dressings remained dry and intact.

Over 80 minutes, the patient remained comatose with a profound high-anion gap metabolic acidosis refractory to six ampules of sodium bicarbonate, each containing 44.6 mEq. An IV infusion of dopamine was required to maintain systolic blood pressure above 90 mm Hg. Despite 80 minutes of resuscitative efforts the patient suffered a terminal bradycardic cardiopulmonary arrest from which she could not be resuscitated. Arterial blood gas analysis at the time revealed pH = 7.05, PO_2 = 197, PCO_2 = 44, base excess = −17 mmol per liter, and CO_2 content = 13 mmol per liter.

Necropsy revealed no obvious anatomic cause of death. Premortem cultures of left hip aspirate, urine, and blood were negative. Postmortem blood and pulmonary alveolar fluid cultures were also negative. The lungs were mildly congested with no evidence of bronchopneumonia or acute pulmonary embolism. The heart was slightly enlarged and contained a few small anterior myocardial hemorrhages, caused by cardiopulmonary resuscitation. Microscopic sections of the myocardium revealed widespread focal myocardial fibrosis consistent with small vessel ischemia, i.e., diabetic microangiopathic cardiomyopathy (6–9). However, the most recent of the small lesions was at least 3 weeks old, and not consistent with acute myocardial infarction. The coronary arteries were slightly calcified but widely patent throughout.

A postmortem serum specimen was analyzed for total iodine content, i.e., I_2 and I^- moieties, utilizing the known iodine-catalyzed reduction of ceric ammonium sulfate by arsenious oxide (10). A serum total iodine concentration of 7,000 μg per 100 ml, 1,000 times the normal level of 5–8 μg per 100 ml, was present. This represented the sum of free and protein-bound iodine as the microcatalytic reaction sequence is preceded by acid hydrolysis of serum total protein.

DISCUSSION

This patient died suddenly after surgical drainage of an infected hip. Necropsy failed to reveal a definite anatomic cause of death. She had been hypertensive and diabetic, with evidence of significant small vessel coronary artery disease, i.e., left-bundle branch block and numerous foci of myocardial fibrosis with no evidence of acute myocardial ischemia. Although systolic time intervals, ejection fraction, and other parameters of left ventricular performance are frequently abnormal in diabetic patients with subclinical heart disease (11, 12), such disturbances, in and of themselves, could not account for her rapidly progressive cardiovascular collapse. Sudden arrhythmogenic cardiopulmonary arrest has been reported in up to 10% of diabetic patients with diabetic autonomic neuropathy (13), a peripheral dysautonomia syndrome characterized by postural hypotension, impotence, nocturnal diarrhea, and/or absence of evoked sinus arrhythmia (14). Primary respiratory arrests have also occurred in these patients during or immediately after administration of narcotics, sedatives, hypnotics, or general anesthesia (15). Neither autopsy findings nor clinical history were suggestive of dysautonomia in our patient.

Systemic iodine/iodide toxicity seemed to be the cause of death. Iodine, atomically the heaviest of the four common halides, serves two important biologic functions. First, iodine in thyroxine (T4) and triiodothyronine (T3) regulates basal intracellular metabolism. Second, as co-substrate for neutrophilic lysosomal myeloperoxidase, inorganic iodide undergoes covalent linkage to phagocytized bacterial cell surface glycoproteins, thereby potentiating the bactericidal capacity of polymorphonuclear leukocytes.

Given the fact that iodide in its organic form tightly regulates cellular metabolism through unidentified biophysical mechanisms, it is not surprising that intracellular uptake of a one thousand-fold excess of this halide can fatally perturb cellular metabolism. Acute elevation of extracellular inorganic iodide concentrations above 10^4 μg per 100 ml can be rapidly fatal within hours (16, 17). Early clinical signs of acute systemic iodine/iodide toxicity stem from stimulation of exocrine gland secretion producing rhinorrhea, conjunctivitis, and a serous, exudative cough. Our patient developed these symptoms approximately 6 hours after P.I.S. irrigation was begun.

The late, preterminal phases of acute systemic iodine/iodide toxicity include a high anion gap metabolic acidosis, thought to be lactic acid mediated (1), acute respiratory distress, and congestive heart failure. Death usually supervenes within hours secondary to cardiogenic shock. Even with attempts at emergency hemodialysis, mortality exceeds 80% (1–3). Lavelle reported serum iodine levels (as iodide) of 10,000–40,000 μg/dl in burned patients treated with povidone-iodine applied every 8 hours. These patients developed severe metabolic acidosis and renal dysfunction (2). Pietsch reported one case with a serum iodide level of 48,000 μg/dl, accompanied by fatal cardiopulmonary arrest (3).

The minimum lethal dose of iodine in humans is unknown. Faddis et al. (18) reported an 11% mortality associated with intra-articular injection of commercial P.I.S. in rabbits where peak predicted serum iodine concentrations reach 2,500 μg/dl. In our patient, the serum total iodide level was 7,000 μg/dl. Since this specimen was obtained 12–14 hours post mortem, peak antemortem serum total iodide levels may well have been substantially higher. Our postulate is based on iodine's known delayed adsorptive and penetrative action through a variety of biologic membranous structures, including glycolipid membranes, eggshells, and intact skin (19–22). Our patient absorbed some 800 ml of one-quarter strength Betadine™ solution used for continuous postoperative hip wound irrigation and manifested all the classical signs of acute systemic iodine/iodide toxicity.

CONCLUSIONS AND RECOMMENDATIONS

Elemental iodine, I_2, is a highly effective topical antiseptic at concentrations equal to or above 0.5 ppm (50

μg/100 ml). Iodophors, i.e., solutions of complex iodine containing anionic and nonionic detergents, contain low free I_2 levels in the range of 0.8–1.2 ppm (80–120 μg/100 ml [23, 24]). Betadine™ prep solution is an iodophor of iodine, polyvinylpyrrolidone (PVP), and detergent.

Despite the low free I_2 levels, standard 10% P.I.S. nonetheless contains a vast reservoir of total available I_2 which, if absorbed systemically, can lead to serious and even fatal toxicity. Therefore, we caution against the use of large quantities of P.I.S. for continuous or intermittent wound irrigation and we recommend that clinicians recognize the potential for serious toxicity when treating patients with iodophor-containing irrigation solutions. Serial serum iodine determinations may help identify incipient toxicity.

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