Propofol-associated Rhabdomyolysis with Cardiac Involvement in Adults: Chemical and Anatomic Findings

Edward B. Stelow, Vandita P. Johari, Stephen A. Smith, John T. Crosson, and Fred S. Apple

Propofol, a central-acting sedative agent, has been implicated in the development of rhabdomyolysis in children. We describe two adults who developed rhabdomyolysis after receiving high rates of propofol infusion. Rhabdomyolysis of both skeletal and cardiac muscle was suggested in both patients by marked increases of creatine kinase (>170 000 U/L) and cardiac troponin I (11 and 46 μg/L in patients one and two, respectively). Creatine kinase and cardiac troponin I values were highly correlated in each patient (r = 0.786 and 0.988 in patients one and two, respectively). Autopsy of one patient confirmed the diagnosis of skeletal and cardiac rhabdomyolysis.

Rhabdomyolysis is a clinical entity that evolves after skeletal muscle injury. The symptoms and signs are secondary to muscle injury and the effects of the release of toxic intracellular contents. They include muscle weakness, myoglobinuria, and renal failure. The causes of the initial injury can range from trauma to venom (1, 2). Drug-induced rhabdomyolysis has been reported as resulting from many possible agents, including the use of propofol for sedation of children in the intensive care unit (3–8). We present two cases in which adults developed rhabdomyolysis after receiving high infusion rates of propofol for extended periods of time. We use chemical and anatomic findings to demonstrate rhabdomyolysis secondary to both skeletal and cardiac muscle injury and secondary acute renal failure.

Case Reports

CASE 1

The patient was a 47-year-old white woman with a long history of steroid-dependent asthma for which she had been intubated twice previously. She presented after worsening shortness of breath at home that had not been relieved with multiple nebulizer treatments. Her past medical history was significant for obesity, depression, gastroesophageal reflux disorder, herniorrhaphy, cholecystectomy, and steroid-induced myopathy. She had no known drug allergies. She was medicated at home with theophylline, prednisone, albuterol, and zafirlukast. Upon reaching the emergency department (ED), she had one-word dyspnea that was not relieved with nebulizer therapy. She was hypertensive, tachycardic, and tachypneic; however, she was afebrile. Her oxygen saturation while receiving oxygen therapy by face-mask was 87–92% before it rapidly began to worsen. It improved quickly after a difficult intubation that lasted nearly 10 min. The patient received intravenous corticosteroids, midazolam, albuterol, vecuronium, and succinylcholine in the ED. She also received lidocaine for multiple premature ventricular contractions after her hypoxic episode. An electrocardiogram taken at that time was without signs of infarct or ischemia. Because of a possible infiltrate on her chest x-ray and an increased white blood cell count, the patient received ceftriaxone. She was admitted to the medical intensive care unit (MICU) where she was treated with albuterol, ipratropium, intravenous corticosteroids, ceftriaxone, and theophylline. Propofol was used for sedative purposes and was to be “titrated to desired effect.” She remained afebrile and was stable with good urine output throughout the next day while her propofol was infused at 200 μg · kg⁻¹ · min⁻¹. An attempt to wean her ventila-
tor support was unsuccessful. The next morning, the patient was afebrile and stable. Her chest x-ray demonstrated a possible worsening infiltrate, and her antibiotic was changed to trovafloxacin. In the morning, serum creatinine and urea did not demonstrate change in renal function. Later that morning, her urine darkened and was positive for blood by reagent strip. No cells were seen. Her creatine kinase (CK) activity (Fig. 1A) was increased at 3900 U/L (reference interval, 40–200 U/L). Her cardiac troponin I (cTnI) concentration (Fig. 1A) was within the reference interval (<0.8 μg/L). She was treated with fluid, diuretics, and bicarbonate therapy. In the afternoon, hyperkalemia, increased creatinine, metabolic acidosis, and hypocalcemia were present. Her CK activity, measured 11 h after the first, was 171 000 U/L, reflecting a 50-fold increase, and her cTnI concentration was increased at 1.4 μg/L. Her urine output decreased, and she became anuric early the next morning. Throughout the day, she was treated with diuretics, fluid replacement, calcium replacement, and bicarbonate therapy. Her white blood cell count increased. She became hypotensive and required dopamine and phenylephrine. Her creatinine concentration continued to increase, and her hyperkalemia and metabolic acidosis worsened. The following morning, propofol was discontinued; her serum CK was 762 000 U/L and her cTnI concentration was 4.0 μg/L. With her worsening hyperkalemia, arrhythmias and episodes of ventricular tachycardia developed, followed by cardiac arrest. Severe hypotension persisted for 15 min before a supraventricular rhythm was re-established. Hemodialysis was started to treat severe hyperkalemia. During this time, her temperature rose to 103.1 °F. She was treated with continuous hemodialysis, calcium, bicarbonate, and phenylephrine and was given dantrolene for possible malignant hyperthermia. Her hyperkalemia worsened nonetheless. Supportive therapy was continued through the night. The following morning, neurology was consulted, who deemed return of previous neurologic status very unlikely because of major anoxic brain injury. Supportive therapy was withdrawn, and the patient expired. Autopsy was performed.

CASE 2
The patient was a 41-year-old white man with a history of asthma for which he had been admitted multiple times but had never been intubated. He presented with worsening shortness of breath that had not been relieved at home with his metered-dose inhalers. Other than his asthma, he had no known medical problems or drug allergies. At home, he was medicated with albuterol, theophylline, zafirlukast, and fludrocortisone, although there was some question of his compliance. He complained of a 1-day history of worsening shortness of breath but did not complain of any symptoms of infection. He was hypertensive and afebrile. Arterial blood gas analysis in the ED demonstrated hypercapnia and acidosis. He was intubated without complication and received ketamine, intravenous corticosteroids, lorazepam, and vecuronium throughout his time in the ED before being admitted.

In the MICU, he was placed on propofol infusion to maintain sedation and received ipratropium, albuterol, and intravenous corticosteroids. He remained stable and afebrile throughout his first and second days. On day 2, he was started on low-molecular weight heparin for deep venous thrombosis prophylaxis. On his third day in the MICU, he was afebrile and stable. Fentanyl was added for analgesic purposes. He required propofol infusion at 222 μg·kg⁻¹·min⁻¹ to maintain sedation for 4 h. On day 4, trovafloxacin was added for a possible infiltrate on his chest x-ray. He remained afebrile with stable vital signs and good urine output. On day 5 in the MICU, his CK activity was 3800 U/L (Fig. 1B; reference interval, 60–300 U/L) in the morning, an increase from 980 U/L the day before. By the afternoon, it was 8090 U/L. Diuretic and fluid therapy was begun after it was noticed that his urine was brown and positive for blood by reagent strip. He was oliguric for a short time, but responded well to diuretic and fluid therapy. Propofol was weaned and discontinued the following morning. His serum myoglobin concentration was increased at 6800 μg/L (reference interval, 0–85 μg/L). Over the next 4 days, the patient’s CK activity and cTnI concentration (Fig. 1B) continued to rise to maximum values of 204 000 U/L and 46 μg/L, respectively. Echocardiography demonstrated globally reduced left ventricular function without a focal lesion. His CK activity and cTnI concentration returned to normal over the next few days.

**Materials and Methods**
CK activity was measured with a Vitros analyzer (Johnson & Johnson). The reference (normal) intervals were 60–300 U/L (males) and 40–200 U/L (females) (9). cTnI was measured on plasma or serum using the Stratus II (Dade Behring). The reference (normal) interval was <0.8 μg/L (10). Myoglobin concentrations were measured at an outside facility by immunoassay with a reference interval of 0–85 μg/L.

An autopsy was performed on patient 1. Representative tissue sections from the lungs, heart, skeletal muscle, and kidneys were fixed in formalin, processed routinely, and embedded in paraffin. All tissues were stained by hematoxylin and eosin and examined by light microscopy.

Statistical analysis was performed using regression analysis on StatView 4.1 on a power Macintosh 6000 computer.

**Results**
CK activities and cTnI concentrations increased in patient 1 (Fig. 1A) and patient 2 (Fig. 1B) after propofol infusions. In both patients, CK activities and cTnI concentrations were highly correlated (r = 0.786 and 0.988, respectively).

Microscopic examination of the skeletal muscle from
Patient 1 showed a disorganization of myofibrils and sarcomeres (Fig. 2). Most of the muscle fibers showed an acute necrotic reaction with swelling, loss of striations, and vacuoles. Many nuclei had degenerated. No inflammatory response was present, and vessels were intact. Sections of the heart revealed numerous focal areas of myofibril degeneration surrounded by an acute inflammatory reaction with macrophages and neutrophils (Fig. 3). Sections through the kidneys showed the presence of reddish brown pigment casts (myoglobin casts) in >50% of the tubular lumens. The tubules were dilated with a marked effacement of the brush border, suggesting severe acute tubular necrosis (Fig. 4).

**Discussion**

These two cases of rhabdomyolysis occurred after high rates of infusion of propofol (200–222 µg·kg⁻¹·min⁻¹). The propofol package insert states a range of infusion necessary for sedation of MICU patients with chronic obstructive pulmonary disease or asthma of 17–75 µg·kg⁻¹·min⁻¹ (n = 49) (11). A review of the literature found that rates between 1 and 142 µg·kg⁻¹·min⁻¹ had been used, with rates >100 µg·kg⁻¹·min⁻¹ being uncommon (12, 13).

Propofol, a central nervous system sedative that interacts with γ-aminobutyric acid aminotransferase receptors (14), has been implicated in the development of rhabdomyolysis in children (4–6, 8). In these cases, the children were intubated for respiratory distress or seizures and were sedated with continuous infusion of propofol. The maximal infusion rate in these cases was between 133 and 449 µg·kg⁻¹·min⁻¹. That these events occurred in children and not in adults was postulated to be because children generally require higher rates of infusion than adults. It should be noted that propofol is not recommended for sedation of children in the ICU setting (15).

In our cases, the clinical diagnoses of rhabdomyolysis were made after the patients were noted to have dark urine. Urinalysis of both patients was positive for blood by reagent strip likely secondary to the passage of myoglobin through the glomerulus (1, 2). Indeed, serum myoglobin was found to be extremely increased in patient 2 (6800 µg/L). CK activity was severely increased in both cases (maximum, 762 000 U/L in case 1 and 204 000 U/L).
in case 2). Increased CK activity is essential for the diagnosis of rhabdomyolysis in cases in which no trauma has occurred, and it reflects the leakage of that enzyme out of the injured myocytes (1, 2).

Injury to the myocardium was demonstrated in both cases by increases in the concentrations of cTnI (maximum, 11.6 μg/L in case 1 and 46.4 μg/L in case 2). cTnI is found exclusively in cardiac muscle (16). Increased concentrations of cTnI in serum, even during skeletal muscle injury, are indicative of cardiac muscle injury (16–19). Cardiac involvement in rhabdomyolysis has been noted, although it has not been demonstrated using serum chemistry results (20). Nor has cardiac injury been demonstrated in the cases of propofol-induced rhabdomyolysis in children (4–6, 8).

Myopathic changes secondary to pharmacotherapy and the further development of rhabdomyolysis have been well documented (21–29). The anatomic findings in case 1 support this etiology because there was such ubiquitous involvement of skeletal and cardiac muscle. The lack of inflammatory infiltrate confirms the acuity of this process. The findings in the kidneys are secondary to muscle destruction because myoglobin is nephrotoxic and depletes renal adenine nucleotide pools and inhibits proximal tubular cell proliferation (30, 31). The severe renal involvement in case 1 gives evidence of the massive rhabdomyolysis that occurred.

The etiology of the rhabdomyolytic process in both of our cases is more difficult to establish. In general, there are many possible etiologies of rhabdomyolysis, the most common being trauma, seizure, and alcohol use (1, 2). Infection, drugs, and toxins have also been implicated (1–8, 21–29, 32–39). Neither of our cases had a history or evidence of trauma. Although patient 1 experienced an hypoxic event in the ED, it seems very unlikely that this could have caused rhabdomyolysis. Both patients had otherwise stable oxygen and hemodynamic status before they developed rhabdomyolysis. Infection was considered in both cases, and it can predispose asthmatics to bronchospasm. In addition, patients who are intubated are at increased risk for infection. Neither of our patients developed a clinically obvious infection, however, and the anatomic findings in patient 1 did not suggest infection. Furthermore, neither patient showed the signs of the degree of infection one would expect to account for the overwhelming rhabdomyolysis that developed.

Both patients were given multiple medications throughout their stay in the MICU before they developed rhabdomyolysis. Steroids, vecuronium, succinylcholine, and theophylline have all been implicated in the development of rhabdomyolysis (2, 3, 24, 27, 33–39). Neither of our patients received excessive doses of any of these medications, and the myopathy that has been demonstrated with most of those drugs seems insufficient to have caused the massive rhabdomyolysis that occurred in our two patients.

In both cases, it is essential to consider the use of corticosteroids, especially because the first patient we presented had a history of steroid myopathy. The acute and necrotizing myopathy that can develop in patients who receive high doses of corticosteroids for asthma in the MICU has been well documented (33–39). This myopathy may be induced by the subsequent infusion of neuromuscular-blocking agents, although it has also been described in patients who received subsequent infusions of propofol alone (35). That none of those patients developed the severe rhabdomyolysis that occurred in our patients may be attributable to the higher doses of propofol that our patients received. If these cases developed in part because of the corticosteroid treatment given, it might support the theory of “priming” and “triggering” factors. In such a case, high-dose propofol would be the myotoxic triggering factor after substantial priming factors have occurred (36).

Consistent with the role of propofol in the development of rhabdomyolysis in our two cases are the facts (a) that cases of propofol-induced rhabdomyolysis have been reported in children who require higher rates of infusion than adults; (b) that the adults in our cases required higher rates of infusion than are typical; and (c) that there is no other sufficient cause to explain the rhabdomyolysis that developed in our cases. How propofol infusion is related to subsequent development of rhabdomyolysis remains unclear. It appears to be idiosyncratic and dose-related and may be potentiated in the critical care setting by the use of high-dose steroids in asthmatic patients.

References