pism, bathmotropism) are mediated via H1 and H2 receptors. Vigorito et al. showed, in a human model, that the IV administration of histamine could elicit two different reactions. In a subgroup of patients with atypical angina or valvular heart disease and normal coronary arteries, the stimulation of H1 receptors induced vasodilation of small coronary resistance vessels. However, in a substantial proportion of patients with vasospastic angina independent of coronary artery disease, histamine provoked vasoconstriction of large capacitance coronary arteries. This finding supports the role of the systemic and local release of histamine during anaphylaxis complicated by coronary vasospasm. Ginsburg et al. in a model of isolated human epicardial coronary arteries, showed that histamine has a very potent vasoconstrictive effect, probably mediated via H1 receptors, whereas H2 receptor stimulation induces vasodilation. The vasoconstrictive effect of histamine in patients with vasospastic angina and morphologically normal coronary arteries is most probably the result of a defective endothelial nitric oxide-mediated vasodilation due to subclinical early coronary atherosclerosis. Although coronary vasospasm has been reported during allergic reactions against wasp stings, antibiotics, nonsteroidal anti-inflammatory drugs, glafenine, and contrast agents, to our knowledge this is the first reported case initiated by a locally administered substance.

In conclusion, anaphylactic reactions can cause such major hemodynamic changes that unmask previously unknown coronary disease. In such situations, fast recovery from the extreme peripheral vasodilation and tachycardia is crucial. On the other hand, the massive release of potent coronary vasoconstrictive mediators may lead to coronary vasospasm, mimicking acute myocardial infarction. Coronary angiography may be needed to define coronary anatomy. Immunologic identification of the causative factor is crucial in order to prevent similar catastrophes in an anaphylactic patient.

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False Elevation of Serum Creatinine Following Skin Absorption of Nitromethane Complicates the Clinical Diagnosis of Rhabdomyolysis*

Andrea Gabrielli, MD and Catherine Hamnett-Stabler, PhD

A patient had extensive blunt trauma from a high-speed crash in which nitromethane fuel erupted from the fuel tank and soaked into his protective multilayer jumpsuit. The clinical diagnosis was complicated because the absorption of nitromethane fuel through the skin and by inhalation falsely increased the serum creatinine value when a modified Jaffe reaction was used in the laboratory. This spurious value was “unmasked” by the use of an enzymatic method to measure the serum creatinine level. A high serum creatinine value disproportionate to the level of BUN and recent skin exposure to nitromethane were the clinical indications that suggested the differentiation of massive rhabdomyolysis from spurious hypercreatinemia. This spurious value was a confounding factor in the diagnosis of crush syndrome and rhabdomyolysis.

(CHEST 1998; 113: 1419-22)

Key words: absorption; nitromethane; rhabdomyolysis; skin

Rhabdomyolysis results when skeletal muscle is injured and toxic intracellular components are released into the systemic circulation. Biochemical hallmarks of this syndrome include increased serum creatine kinase level,

*From the Departments of Anesthesiology (Dr. Gabrielli) and Pathology, Immunology, and Laboratory Medicine (Dr. Hamnett-Stabler), University of Florida College of Medicine, Gainesville.

Manuscript received July 17, 1997; revision accepted October 16, 1997.
myoglobinemia, and myoglobinuria. This case report describes a patient whose clinical picture suggested a diagnosis of rhabdomyolysis secondary to blunt trauma of the chest and extremities; however, a high serum creatinine concentration and normal BUN concentration at admission complicated the clinical diagnosis.

**CASE REPORT**

A 25-year-old man was involved in a crash, at an estimated speed of 290 miles per hour, while professionally racing a dragster. Emergency personnel at the race track noted that the patient was awake and that his protective, multilayered jumpsuit was partially burned and that his jumpsuit and underwear were soaked with fuel from the car’s fuel tank. The jumpsuit was removed, the patient was stabilized, and then he was transferred by air ambulance to the local hospital. On admission to the emergency department, his Glasgow coma score was 15 and he had retrograde amnesia as a result of the accident. His blood pressure was 107/52 mm Hg, heart rate was 92 beats/min, and respiratory rate was 25 to 30 breaths/min. Multiple bruises and lacerations were present; there was no sign of burn injury to his skin.

The patient was in moderate respiratory distress with an oxygen saturation level between 90 and 95% while breathing 100% oxygen through a nonbreathing face mask. A moderate amount of hemoptysis was noted. The patient was electively intubated for airway protection, and a fiberoptic tracheobronchoscopy was performed to assess the integrity of the tracheobronchial tree. A CT scan of the head was normal. Radiographic studies showed a C-7 spinous process fracture, patellar avulsion without fracture, and evidence of right and left pulmonary contusions with a small pneumomediastinum and subcutaneous emphysema, without evidence of pneumothorax. Because the patient’s injuries resulted from a high-speed crash, and a pneumomediastinum was present, an aortic arch angiogram was done, which was normal. The ECG showed sinus tachycardia. Pertinent laboratory test results included the following values; the presence of hemoglobin in the urine; creatinine, 8.6 mg/dL (normal, 0.5 to 1.2 mg/dL); and BUN, 12 mg/dL (normal, 10 to 20 mg/dL) (Table 1).

The patient was transferred to the surgical ICU. Three hours later, repeated laboratory test results were a creatinine level of 17.5 mg/dL and a BUN value of 13 mg/dL. A toxicology screening was positive for benzo diazepines and opiates, which had been administered during the intubation procedure. Five hours after surgical ICU admission, the creatinine level was 14.2 mg/dL and the BUN value was 11 mg/dL. An osmolar gap of 2 did not suggest the presence of an un-ionized, low-molecular weight intoxicant. The 24-h urinary creatinine level was 2.5 g with a volume of 4,500 mL. For a serum creatinine concentration of 14.2 mg/dL, the calculated creatinine clearance was equal to 5.5 mL/min. Even with the extremely low creatinine clearance, the patient’s acid-base profile and urine output were normal. Creatinine kinase activity increased and peaked at 3,180 U/L on day 5 (Table 1). Myoglobin was still not found in the urine. An echocardiogram 1 day after admission showed no signs of myocardial contusion. Four days after admission, the patient’s general condition and chest contusion had improved, and the pneumomediastinum had receded spontaneously. The patient was extubated and transferred to the ward. The patient’s serum creatinine concentration was followed up daily and decreased from a peak of 17.5 to 0.8 mg/dL in 13 days (Table 1). He was discharged in good clinical condition 10 days after admission to the emergency department.

**DISCUSSION**

Renal failure is the most common cause of morbidity with rhabdomyolysis. The mechanisms of renal injury may include renal vasoconstriction, intraluminal cast formation, and cytotoxicity due to heme production. Renal vasoconstriction is secondary to intramuscular third spacing, cytokine-endotoxin cascades released from muscle injury and necrosis, and heme-pigment nitric oxide scavenging action.

The formation of intraluminal casts of myoglobin induces tubular stasis. Cast formation is facilitated by volume depletion, filtrate reabsorption, and loss of solubility secondary to the acidic urine environment. Renal cytotoxicity from heme pigment is related to direct cellular ischemic damage of the proximal tubule and reperfusion injury.

Dehydration is a common clinical factor in patients who develop acute renal failure from crush injury. Dehydration enhances renal vasoconstriction and the concentration of toxic metabolites in the proximal tubule lumen.

At the ultrastructural level, crush-related rhabdomyolysis implies an initial pressure stress insult secondary to decreased external microcirculation and, therefore, decreased oxygen delivery to the cells. Intracellular ischemia results; this ischemia then triggers a chain reaction of

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**Table 1—Laboratory Test Results for Patient**

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Normal Range</th>
<th>Admission</th>
<th>3-h PA*</th>
<th>5-h PA*</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>0.5-1.2 mg/dL</td>
<td>8.6</td>
<td>17.5</td>
<td>14.2</td>
<td>13.9</td>
<td>8.6</td>
<td>5.1</td>
<td>3.1</td>
<td>1.9</td>
<td>1.3</td>
<td>0.9</td>
<td>0.8</td>
</tr>
<tr>
<td>BUN</td>
<td>19-40 mg/dL</td>
<td>12</td>
<td>13</td>
<td>11</td>
<td>11</td>
<td>8</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>11</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>5-180 U/L</td>
<td>—</td>
<td>—</td>
<td>1,268</td>
<td>1,852</td>
<td>3,160</td>
<td>2,664</td>
<td>3,180</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>0-2.9 mg/mL</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>26.7</td>
<td>36.5</td>
<td>2.3</td>
<td>6.2</td>
<td>5.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Sodium</td>
<td>135-145 mEq/L</td>
<td>144</td>
<td>141</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>140</td>
<td>143</td>
<td>138</td>
<td>139</td>
<td>139</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.0 mEq/L</td>
<td>3.2</td>
<td>4</td>
<td>4.3</td>
<td>3.8</td>
<td>3.5</td>
<td>3.9</td>
<td>3.7</td>
<td>3.9</td>
<td>4</td>
<td>4.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Chloride</td>
<td>95-105 mEq/L</td>
<td>108</td>
<td>115</td>
<td>112</td>
<td>113</td>
<td>111</td>
<td>109</td>
<td>106</td>
<td>102</td>
<td>101</td>
<td>105</td>
<td>—</td>
</tr>
<tr>
<td>CO₂</td>
<td>24-32 mEq/L</td>
<td>22</td>
<td>19</td>
<td>17</td>
<td>19</td>
<td>22</td>
<td>25</td>
<td>27</td>
<td>25</td>
<td>31</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>Serum osmolality</td>
<td>275-295 mOsm/kg</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>289</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>50-1,100 mOsm/kg</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>826</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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</tbody>
</table>

*PA = postadmission.
increased sarcolemmal sodium and calcium influx, intracellular acidosis, adenine triphosphate depletion, and cell death. Restoration of blood flow, when feasible, allows the movement of neutrophils into the necrotic area and the release of free radicals in the cell microenvironment. Cell death is enhanced through a mechanism of reperfusion injury. The increase in creatinine kinase and creatine is considered an intravascular marker of such events.

The concentration of creatinine in muscle is approximately 4 mg/100 g of tissue. The patient in this report weighed 80 kg. Calculating the extracellular space as 60% of total body weight, damage to 1 kg of muscle would have increased the serum creatinine concentration to 0.12 mg/dL. It is impossible to evaluate the exact amount of muscle damage. However, even if one assumes that 10% of the body muscular mass was damaged and its content was released completely in 24 h into the extracellular space, the creatinine should not have increased by more than 1.2 mg/dL.

Another mechanism that could explain the increase of serum creatinine is the conversion of intracellular creatine and creatine phosphate to creatinine. This conversion rate is <3%/d in patients with a normal pH level and a temperature of 38°C, and would have been responsible for only a negligible increase in this patient.

A high creatinine-to-BUN ratio was described in 903 crush-injury patients with acute renal failure. These patients had an average creatinine-to-BUN ratio of 0.0187 within 24 h of the injury. Their median creatine kinase activity was 21,775 U/L, 13 times higher than the initial creatine kinase activity in our patient. These patients were predominantly young men, as was the reported patient, who because of greater muscle mass than average have more creatinine release after trauma. The creatinine-to-BUN ratio of the reported patient was 0.7. In a series of patients with creatine kinase activity similar to ours, the average serum creatinine concentration was between 1.5 to 2.7 mg/dL.

Other biochemical features associated with severe crush injury syndromes are hyperkalemia and often severe hypocalcemia. Neither of these conditions was present in the reported patient.

What made the reported patient’s clinical presentation unique was the high creatinine level on admission; this level peaked in a manner similar to that observed in patients with untreated chronic renal failure. Thus, despite the circumstances of the accident, the initial clinical presentation, the BUN, and the creatine kinase activities did not correlate with the very high creatinine level. In particular, the maximum creatine kinase activity observed at 3,180 U/L within 5 days suggests clinically mild rhabdomyolysis; this was confirmed by the lack of myoglobin in the urine. Additionally, none of the other metabolic markers were suggestive of renal function impairment. For example, despite the calculated low creatinine clearance of 5.5 mL/min, the urine osmolality was “appropriately” concentrated at 826 mOsm/kg, and the urine output was optimal. After repeated measurement of creatinine confirmed the early high concentration, the presence of an interfering substance was suspected.

The Jaffe reaction that was used to measure creatinine is nonspecific and other chemicals besides creatinine can react with the picric acid, thus leading to an apparent increase in the creatinine concentration. A number of modifications to the assay are in use today to lessen this problem. Chemicals known to cause this type of interference include glucose, acetone and ketoacids, ascorbic acid, as well as some of the cephalosporins. Most of these interfere when present in high concentrations. This patient was not receiving any of the drugs known to cause this increase, and his glucose level was not sufficiently elevated to cause such an increase. Therefore, one may suppose that interference by these chemicals was not a factor in this case. A review of the fuel mixture that had saturated this patient’s clothing at the accident scene showed the fuel to be 95 to 98% nitromethane with 2 to 5% methanol. Short-distance racing cars and model engines use this type of fuel. This patient, it may be suspected, had absorbed a substantial amount of nitromethane both through the skin and by inhalation.

Nitromethane is used as a stabilizer for chlorinated hydrocarbons, as a compound of special fuels for internal combustion engines, and as a solvent. A colorless and odorless fluid, nitromethane is flammable, and when ignited, it burns with an almost invisible, colorless flame that often self-extinguishes or can be easily extinguished by water. Resins with extensive commercial applications, such as vinyl, epoxy, and polyamide and acrylic polymers, are soluble in nitroaraffins, such as nitromethane.

Nitromethane can explode if subjected to a severe shock while under confinement in heavy-walled pressurized containers. Heating a solution of nitromethane to approximately 350°C also may result in an explosion. The combination of high pressure and temperature is used as an energy source for short-distance, high-speed vehicles, as well as in top-fuel race cars.

The toxicology of nitromethane has been extensively studied in animal models. The most common lesions described after acute intoxication are tubular cell edema in the kidney and liver and spleen hemorrhagic congestion. A massive acute overdose of nitromethane in animals results in death and is preceded by acute excitations of the convulsive type. A study of skin and mucosal toxicity with chronic exposure to nitromethane in animal models showed only dry skin because of the defatting action of the compound. The American Conference of Governmental Industrial Hygienists has established 100 ppm as the threshold limit for nitromethane vapor exposition per 8 h.

Only one case of nitromethane toxicity has been reported previously. In this case the patient ingested model airplane fuel in a suicide attempt. The concentration of nitromethane in this type of fuel is only 10 to 30%. A high serum creatinine level (8.0 mmol/L), which was measured using a modified Jaffe reaction, was reported in this case. A modified Jaffe reaction also is used in the laboratory for measuring the values for the patient reported in this study. As with many of the chemicals known to interfere with methods using this reaction, nitromethane contains a reactive methyl group, which reacts with the picric acid used in the assay. As in the previously reported case, when samples from the reported patient were tested using a
more specific enzymatic method, normal creatinine concentration was found. As far as can be determined, this is the first time that such an interference with the analytical method can be attributed to skin absorption and inhalation of nitromethane. In the case reported here, the history of severe blunt trauma associated with elevated creatine kinase activity complicated the clinical diagnosis.

Nitromethane is considered by most industrial toxicologists as only slightly toxic when ingested and even less toxic when inhaled or absorbed via the skin. This case report demonstrates that skin absorption of nitromethane can interfere with the measurement of serum creatinine when a modified Jaffé reaction is used. This interference may complicate the clinical picture. As far as can be determined, this is the first case that describes such interference in a patient who had absorbed nitromethane through the skin.

ACKNOWLEDGMENT: The authors thank Anita S. Yeager for editorial assistance.

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