Toxicant-Induced Rhabdomyolysis

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The first known reference to rhabdomyolysis is said to be in the Bible in the Book of Numbers, [1] in which an illness is described that occurred in Israelites after eating hemlock-fed quail. Rhabdomyolysis is a potentially life-threatening syndrome that can develop from a variety of causes. The term "Rhabdomyolysis" literally translates to "dissolution of striped [skeletal] muscle." It is the final common pathway of a number of different processes, all of which end in skeletal muscle injury. An elevated plasma creatinine kinase (CK) level is the most sensitive laboratory finding pertaining to muscle injury; whereas hyperkalemia, acute kidney injury, and compartment syndrome represent the major life-threatening complications [2]. The clinical and biochemical syndrome of rhabdomyolysis occurs when skeletal muscle cell disruption causes release of muscle cell contents (CK, lactate dehydrogenase, aldolase, myoglobin, purines, potassium, and phosphates) into the interstitial space and plasma. Although direct mechanical trauma, compression, excessive muscle activity, and ischemia are frequent causes, direct xenobiotic-induced rhabdomyolysis results from toxic insult to the cell membrane, affecting its ability to maintain ion gradients. Although rhabdomyolysis does not indicate irreversible necrosis of muscle, life-threatening illness and multi-organ insufficiency may result [3, 4].

Most cases of rhabdomyolysis in adults are multifactorial, but those related to poisoning are generally due to one of the three clinical scenarios.

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J. Brent et al. (eds.), *Critical Care Toxicology*,
DOI 10.1007/978-3-319-17900-1_106

The first includes patients that develop a xenobiotic-induced sympathomimetic or hyperadrenergic state that may include seizures and/or psychomotor agitation. Second are patients with significant decreased levels of consciousness who develop muscle injury from unrelieved pressure on gravity-dependent body parts and prolonged immobilization. There are unique drugs or toxins that cause rhabdomyolysis due to direct toxicity. Examples of these unique causes include ethanol, doxylamine [5] intoxication, use of lipid-lowering agents, and ingestions of the mushroom *Tricholoma equestre* [6].

Pathophysiology

Although there are a large number of drugs or toxins that can cause rhabdomyolysis, the pathogenesis appears to follow a final common pathway, ultimately leading to myocyte destruction and release of muscle components into the circulation. In the normal myocyte, the sarcolemma has a thin membrane that encloses striated muscle fibers and contains numerous pumps that regulate cellular electrochemical gradients. The intercellular sodium concentration is normally maintained at 10 mEq/L by a sodium-potassium adenosine triphosphatase (Na/K-ATPase) pump located in the sarcolemma [7]. The Na/K-ATPase pump actively promotes sodium efflux from the cell causing the interior of the cell to be electronegative. This electrochemical gradient result causes calcium efflux via the sodium/calcium exchange. Moreover, low cytosolic calcium levels are also maintained by an active calcium exchanger (Ca2+ ATPase pump) that promotes calcium entry into the sarcoplasmic reticulum and mitochondria [8]. The above processes are energy dependent.

Adenosine triphosphate (ATP) depletion, which appears to be the end result of most causes of rhabdomyolysis, results in Na/K-ATPase and Ca2+ ATPase pump dysfunction resulting in an increase in cellular permeability. Sodium, chloride, and water movement into the cell then is due to either plasma membrane disruption or reduced ATP production [3, 4, 9–11]. Accumulation of sodium in the cytoplasm leads to an increase in intracellular calcium concentration (which is normally very low relative to the extracellular concentration). This excess calcium then increases the activity of intracellular proteolytic enzymes that degrade the muscle cell. As the myocyte degenerates, large quantities of potassium, aldolase, phosphate, urate, creatinine kinase, lactate dehydrogenase, aspartate transaminase, and myoglobin leak into the circulation [7, 9, 10].

When myoglobin is released from myocytes, it becomes protein bound (50% at serum concentrations < 23 mg/dL) and is rapidly metabolized to bilirubin [12]. Under physiological conditions, the plasma concentration of myoglobin is very low (0–0.003 mg/dL). Free myoglobin is rapidly filtered by renal glomeruli, with an elimination half-life of 1–3 h and disappearance from the circulation within 6 h of release [13, 14]. However, if more than 100 g of skeletal muscle is damaged, the circulating myoglobin levels exceed the protein-binding capacity of the plasma and can precipitate in the glomerular filtrate [2]. Myoglobin may be released in sudden, massive amounts making it detectable before creatinine kinase [15] (Fig. 1).

Drug-Induced Rhabdomyolysis

Examples of drugs, toxins, or other agents that are associated with rhabdomyolysis are listed in Table 1 [16]. Toxicant-induced agitation, seizures, withdrawal, and hyperthermia are typical underlying features leading to rhabdomyolysis. Even in the absence of coma or seizures, ethanol ingestion (especially binge drinking) can cause muscle damage and rhabdomyolysis by an unknown mechanism [17]. However, it has been theorized that altered muscle ion homeostasis occurs because of changes in sodium-potassium transport pump activity allowing increased sodium entry into the cell [18, 19]. Nutritional deficiencies, hypophosphatemia, and hypokalemia may be coexistent risk factors for the development of rhabdomyolysis [3, 20, 21]. Cholesterol-lowering drugs of the statin class are also associated with

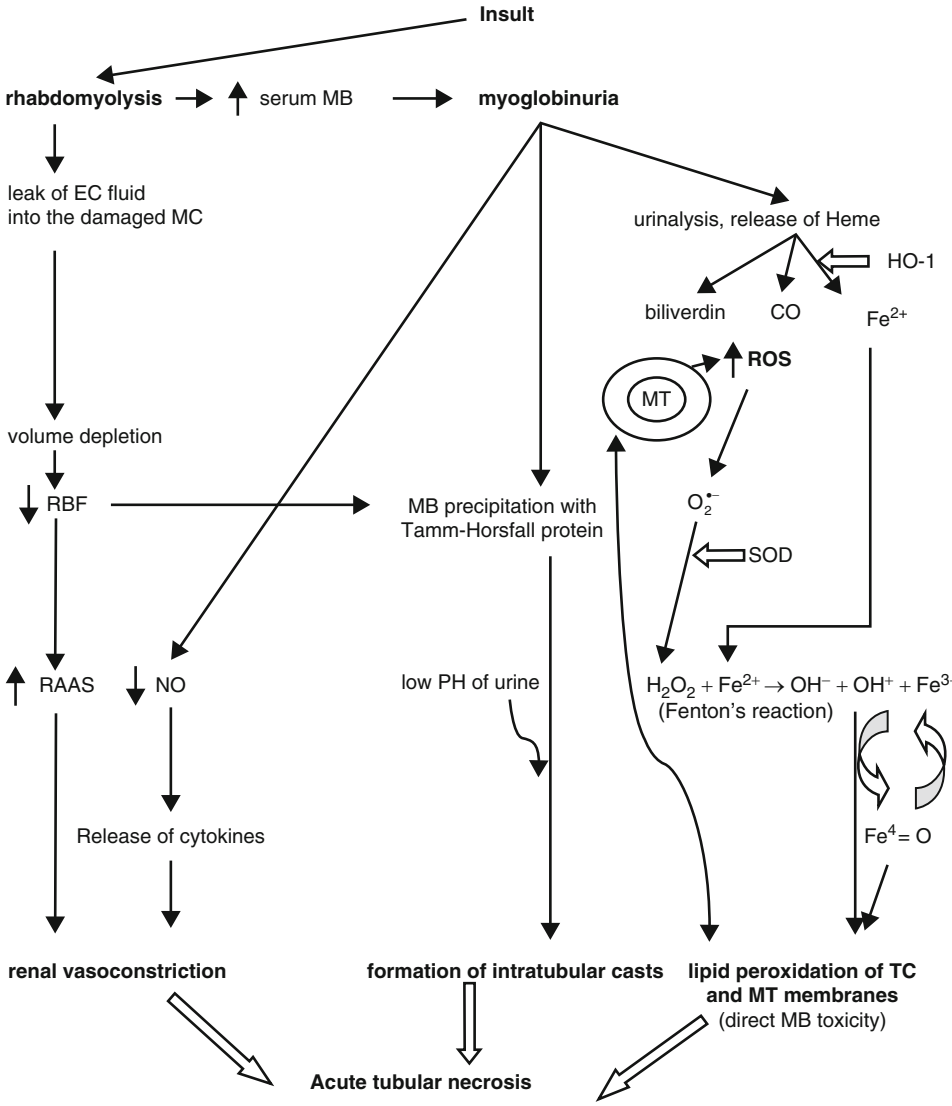

Fig. 1 Pathophysiology of rhabdomyolysis-induced acute kidney injury. *CO* carbon monoxide, *EC* extracellular, Fe^{2+} ferrous iron, Fe^{3+} ferric iron, Fe^{4} O, ferryl iron, *HO-1* heme oxygenase-1, H_2O_2 hydrogen peroxide, *MB* myoglobin, *MC* muscle cell, *MT* mitochondria, *NO* nitric oxide, OH^- hydroxyl anion, $O_2^{\bullet-}$ superoxide radical, $OH^{\bullet}$ hydroxyl radical, *RAAS* renin–angiotensin–aldosterone system, *RBF* renal blood flow, *ROS* reactive oxygen species, *SOD* superoxide dismutase, *TC* tubular cell (Petejova and Martinek [56]. Used through a creative Commons license)

drug-induced rhabdomyolysis in the absence of other major clinical manifestations of toxicity [22]. Other unique and classic causes of rhabdomyolysis include doxylamine [5] intoxication and ingestion of the mushroom *Tricholoma equestre* [Saviuc].

Statins

Statin-associated rhabdomyolysis is rare but a well-known adverse effect of this class of drugs. Statin-induced myotoxicity is dose dependent. The concept of a dose-dependent increased risk

Table 1 Drugs and toxins associated with rhabdomyolysis[16]

Class	Examples
H2 antagonists	Famotidine, cimetidine
Analgesics and anti-inflammatory agents	Salicylates, acetaminophen, propoxyphene, opiates, buprenorphine, ibuprofen, diclofenac, phenylbutazone, sulfasalazine, glucocorticoids, pethidine, colchicine
Anesthetics	Inhalation anesthetics, propofol, ketamine, glutethimide
Antibiotics, antifungals, and antivirals	Chloroquine, hydroxychloroquine, daptomycin, fluoroquinolones, trimethoprim/sulfamethoxazole, amphotericin B, itraconazole, isoniazid, zidovudine, ritonavir, didanosine
Antidepressants, antipsychotics, and mood stabilizers	All classes antidepressants, haloperidol, risperidone, thioridazine, loxapine, amoxapine, lithium, chlorpromazine
Antihistamines and antimuscarinics	Doxylamine, diphenhydramine, all antimuscarinics
Beta-adrenergic antagonists	Oxprenolol, labetalol
Cholesterol lowering	Fibrates, HMG-CoAse reductase inhibitors (statins)
Chemotherapeutic and immunosuppressant medications	Vincristine, cytarabine, mitoxantrone, arsenic trioxide, cyclosporine A, alpha interferon, interleukin 2, azathioprine, tacrolimus, trabectedin, leflunomide
Alcohols and recreational drugs	Ethanol, ethylene glycol, methanol, heroin, methadone, cocaine, amphetamines, LSD, ecstasy, marijuana, PCP, synthetic cathinones
Sedatives/hypnotics	Diazepam, temazepam, lorazepam, chloral hydrate, barbiturates
Miscellaneous	Amiodarone, D-penicillamine, vitamin A, vitamin B6, insulin, nifedipine, phenytoin, valproate, tryptophan, laxatives, diuretics, streptokinase, aminocaproic acid, caffeine, theophylline, terbutaline, vasopressin
Toxins and environmental	Hemlock, hemlock herbs from quail, wild mushrooms (*Amanita phalloides*, *Tricholoma equestre*), snake venoms, Hymenoptera, giant desert centipede, black widow spider, toluene, carbon monoxide, hyperthermia, hypothermia, thujone containing plants (*Artemesia absinthium* [wormwood], *Salvia officinalis* [sage], *Tanacetum vulgare* [tansy], *Achillea millefolium* [yarrow], *Thuja plicata* [red cedar], and *Thuja occidentalis* [white cedar]), seafood poisoning (Haff disease due to freshwater fish, buffalo fish, crayfish, Atlantic salmon, pomfret; palytoxin due to marine reef fish, bottom feeding fish, crabs, anemones)
Tyrosine kinase inhibitors	Sunitinib, imatinib, erlotinib (when combined with simvastatin)

of statin-related muscular adverse effects is supported by the results of a meta-analysis. Overall, the observed excess of rhabdomyolysis was 4 per 10,000 patients with more intensive versus less intensive statin therapy compared with 1 per 10,000 patients on standard statin regimens versus control (at least 2 years follow-up) [23]. Although the exact mechanism of statin-associated myopathy is unclear, there appears to be vulnerability related to gene polymorphism in addition to several intracellular mechanisms. Functional variation of the hepatic uptake transporter SLCO1B1 has been implicated in statin-induced myopathy. An analysis by Carr et al. revealed the SLCO1B1 c.521 T > C single-nucleotide polymorphism to be a significant risk factor for severe myopathy [24]. Meta-analysis showed an association between c.521C > T and simvastatin-induced myopathy, although power for other statins was limited in their study. Pathophysiologically, statins appear to deplete geranylgeranyl pyrophosphate, thereby reducing prenylated Rab. Intracellular vesicle traffic is consequently suppressed inviting mitochondrial dysfunction and ATP depletion [23, 25]. Studies have also suggested that variation in the coenzyme Q2 (COQ2) homologue gene may predispose individuals to statin-induced myopathy. In addition, abnormal mitochondrial respiratory function is caused by statin-induced coenzyme Q10 deficiency [43]. Puccetti et al. demonstrated an association between both rosuvastatin- and

atorvastatin-induced myopathy and the rs4693075 polymorphism in the COQ2 gene [26]. An association of another COQ2 variant (rs4693570) and statin-induced myalgia has also been described [27].

Some concomitant medications appear to increase the risk of statin-associated myopathy. Among the 601 cases of statin-associated rhabdomyolysis investigated by Omar et al. [28], the most common concomitant medications were mibefradil (99 patients) fibrates (80 patients), ciclosporin (51 patients), macrolide antibiotics (42 patients), warfarin (33 patients), digoxin (26 patients), and azole antifungals (12 patients).

Doxylamine

Rhabdomyolysis in uncomplicated antihistamine overdoses is uncommon. Severe cases of rhabdomyolysis following antihistamine exposures typically are associated with the development of seizures and hyperthermia [29–31]. Doxylamine, an over-the-counter drug used primarily as a sleep-inducing agent, however, is associated with rhabdomyolysis in the absence of prolonged sedation, agitation, or delirium or seizures [32]. Early studies reported that the incidence of rhabdomyolysis following doxylamine was relatively low [33]. In contrast, in urban emergency departments in Korea, doxylamine overdose accounts for 25% of visits due to drug overdose [34] and the incidence of rhabdomyolysis ranges from 32% to 77% [5, 35, 36]. In addition, rhabdomyolysis developed in 21.0% (35/169) of patients who had creatinine kinase levels within the reference range at presentation [32].

The mechanism for rhabdomyolysis in doxylamine overdose is uncertain. In the multivariate regression analysis, by Kim et al., the amount of doxylamine ingested and the initial heart rate were reliable associative factors for the development of rhabdomyolysis [Kim]. In a prospective study by Jo et al., looking at doxylamine overdose, their bivariate analysis in patients who developed rhabdomyolysis differed from those who did not in the amount of doxylamine ingested (36.2 vs. 17.2 mg/kg, p 0.003). Initial value of serum Cr (1.3 vs. 0.8 mg/dL, p 0.022) was significantly higher and the arterial pH (7.36 vs. 7.43, p 0.032) was significantly lower in patients with rhabdomyolysis than those without [5]. In their study rhabdomyolysis was common, occurring in 87% of patients who ingested more than 20 mg/kg.

Tricholoma (equestre/flavovirens)

Several cases of massive rhabdomyolysis have been reported since 1993 in France and 2001 in Poland after ingestion of large amounts of an edible and, until then, valuable species of mushroom called *Tricholoma equestre* (common name "Man on Horseback"). Several of these cases of rhabdomyolysis were associated with respiratory complications and myocarditis leading to death [6]. The toxic dose or underlying predisposing factors for susceptibility in humans are unknown. *Tricholoma equestre* toxicity appears to require extremely large doses, in the order of 100–400 g at each meal over repeated meals [37]. The myotoxic component of *Tricholoma equestre* has not been identified. The mushroom contains triterpenoids, a high steroid and aldehyde content, indoles, and acetylenic compounds [38]. The onset is 24–72 h after the last meal, with presenting symptoms of muscle weakness, fatigue, anorexia, and muscle pain in lower extremities, progressing over several days, followed by dark urine.

Water Hemlock

Rhabdomyolysis is common in water hemlock poisoning. Patients often complain of muscle pain and tenderness at the time of presentation. It is likely to occur in patients with recurrent seizures but has also been seen in patients in the absence of seizures, although to a lesser degree. In the absence of seizures, the mechanism of myotoxicity is unknown [39–41].

Cocaine

Cocaine use leads to rhabdomyolysis through psychomotor agitation, seizures, and impaired behavioral responses [42, 43] Serum CK values have been reported up to 100,000 U/L (1700 *u*kat/L). In large doses, cocaine has direct toxic effects on skeletal muscle causing myofibrillar degeneration. In addition, muscle ischemia from vasoconstriction may predispose to further muscle injury. Although crack cocaine is the most reported in the literature, all forms of cocaine use can cause rhabdomyolysis. A prospective case series of patients presenting to an emergency department with complaints related to cocaine use showed a high incidence of cocaine-associated rhabdomyolysis. Of all cocaine users, 24% had rhabdomyolysis, defined by an elevation of creatinine kinase of more than fivefold that of the mean level (>1000 U/L; 17 *u*kat/L). The same study found that only 13% of the patients presenting with rhabdomyolysis experienced any of the classic signs or symptoms (nausea, vomiting, myalgias, muscle swelling and tenderness, weakness) [44].

Patients at highest risk for complications from rhabdomyolysis are patients presenting with signs of sympathomimetic toxicity. A retrospective study showed that patients with acute cocaine intoxication who had admission serum creatinine kinase levels < 1000 U/L (<17 *u*kat/L), a normal serum creatinine concentration, a normal WBC, and no more than one additional risk factor for rhabdomyolysis (i.e., muscular activity, other mind-altering drugs, seizures) were unlikely to develop rhabdomyolysis [45].

Propofol

Propofol is widely used as a short-acting anesthetic and for sedation of critical ill patients. Current recommendations suggest a dosage less than 8 mg/kg/h and application not longer than 2 days in adults [46–48]. Rhabdomyolysis occurs most frequently with high doses of propofol after 96 h of administration [49]. On a molecular level, propofol is toxic for mitochondria and elevates malonyl-carnitine concentrations [50]. It uncouples oxidative phosphorylation and inhibits the respiratory chain at complexes II and IV [51–53]. In particular, fatty acid transport is inhibited by elevated malonyl-carnitine levels that impair entry of long-chain acylcarnitine esters into the mitochondria and failure of the mitochondrial respiratory chain at complex II [53].

Rhabdomyolysis may accompany propofol infusion syndrome, a rare but extremely dangerous complication of propofol administration. Certain risk factors for the development of propofol infusion syndrome are described, most notably propofol doses and durations of administration. Based on the data from case reports and case series, it is not recommended to administer propofol for more than 48 h or infusions more than 4 mg/kg/h (67 mcg/kg/min). Other potential risk factors for the development are critical illness (sepsis, head trauma, status epilepticus, etc.), use of vasopressors and glucocorticosteroids, carbohydrate depletion (liver disease, starvation, or malnutrition), carnitine deficiency, and subclinical mitochondrial disease [54]. The syndrome commonly presents as an otherwise unexplained high anion gap metabolic acidosis (due to elevation in lactic acid), rhabdomyolysis, hyperkalemia, acute kidney injury, elevated liver enzymes, and cardiac dysfunction [54].

Clinical and Laboratory Manifestations

An elevated serum CK is the most sensitive and reliable indicator of muscle injury. Table 2 lists the common features of diagnosis of rhabdomyolysis and subsequent acute kidney injury. The definitive diagnosis of rhabdomyolysis requires an elevation of CK levels to more than five times normal. The isoenzyme CK-MM (found in skeletal and cardiac muscle) is responsible in large part for the elevation in serum CK; the CK-MB fraction (found primarily in cardiac but also in skeletal muscle) should not exceed 5% of the total CK level. Serum CK generally rises 2–12 h after the onset of muscle injury and peaks 24–72 h, after which it declines at the relatively constant rate of 39% of the previous day's value [55]. Creatinine kinase

Table 2 Diagnosis of rhabdomyolysis and subsequent acute kidney injury (Adapted from Petejova and Martinek [56])

Clinical presentation
Muscular weakness, myalgia, swelling, tenderness, stiffness
Fever, feelings of nausea, vomiting, tachycardia
Oligoanuria or anuria in connection with renal damage or in the presence of volume depletion
Signs/symptoms of associated drug/toxin toxicity
Laboratory findings
Serum: creatinine, urea nitrogen, creatinine phosphokinase, myoglobin, ions (potassium, phosphorus, calcium), lactate dehydrogenase, transaminases, acid–base balance
Urine: myoglobin or positive dipstick test without any erythrocytes

values that fail to decrease in this manner suggest ongoing muscle injury.

Serum myoglobin increases within a few hours of muscle injury, before the increase in serum creatinine kinase. Because the metabolism of protein-bound myoglobin to bilirubin and the renal excretion of free myoglobin occurs rapidly, serum myoglobin concentration are typically normal 1–6 h after cessation of muscle injury in the presence of normal renal function [20]. Consequently, absence of myoglobinuria does not preclude the diagnosis of rhabdomyolysis. Variables that determine the presence of myoglobin in the urine include the glomerular filtration rate, the concentration of plasma myoglobin, the degree of plasma protein binding, and the rate of urine production and flow [57–59].

Dark brown urine, positive for blood on a reagent strip but without red blood cells on microscopic examination, indicates the presence of myoglobin [11]. Although the renal myoglobin threshold is 1 mg/dL, the urine does not become discolored until its myoglobin concentration is great than 100 mg/dL. Urine dipsticks containing orthotoluidine react with the globin fraction of hemoglobin and myoglobin. If red blood cells are present, the orthotoluidine reaction does not differentiate hemoglobin from myoglobin. Radioimmunoassay, immunoelectrophoresis, and hemagglutination are more specific than urine dipstick methods but also significantly more expensive [11].

Muscle cell disruption results in the release of potassium, phosphate, and urate. Acidemia and renal insufficiency may increase serum potassium concentrations further. Hypocalcemia, the result of deposition of calcium in the damaged muscle, may be present with or without acute kidney injury. It is usually clinically insignificant, unless it occurs in the setting of severe hyperkalemia or ventricular dysfunction [45]. In approximately 30% of patients with acute kidney injury and rhabdomyolysis, hypercalcemia occurs in the subsequent diuresis phase of the renal impairment. Parathyroid hormone concentrations are typically normal or low, but 1,25-dihydroxycholecalciferol concentrations are much greater in the hypercalcemic patients than in patients who do not develop hypercalcemia [60].

Aldolase, lactate dehydrogenase, and aspartate transaminase activities are frequently elevated as well but only aldolase is specific for muscle injury. Creatinine may be elevated from both renal insufficiency and from the release of creatine from muscle and its spontaneous hydration to creatinine [11].

Complications

Acute Kidney Injury

The primary complication of rhabdomyolysis is acute kidney injury, which occurs in approximately 30% of patients [56, 61]. Risk factors for acute kidney injury in the setting of drug or toxin exposure are less studied than in traumatic or medical-associated rhabdomyolysis. In general, risk factors for acute kidney injury in the presence of rhabdomyolysis include hyperkalemia, hyperphosphatemia, dehydration, sepsis, intravascular volume depletion, high serum myoglobin concentrations, and low myoglobin clearance [18, 56].

The concentration of heme pigments resulting in acute kidney injury is not well understood. At urine pH less than 5.6, myoglobin dissociates into ferrihemate and globin. Ferrihemate depresses renal tubular transport mechanisms and causes a subsequent deterioration in renal function [14, 62]. Myoglobin (molecular weight 17,500 Da)

may interfere with the endogenous vasodilator nitric oxide, causing a decrease in GFR. Myoglobin and other muscle constituents, such as urate, which is metabolized to uric acid, may deposit in the tubules. Other theories include the presence of oxygen free radicals. Animal experiments show that myoglobin causes renal damage when dehydration is present. Contributing factors seem to be concentrated urine with low urine flow and urine pH less than 5.6. Published clinical reviews conclude that patients with hyperkalemia, hyperphosphatemia, high serum myoglobin concentrations, and low myoglobin clearance seem to be at risk for development of acute kidney injury [9, 18, 63–66].

Other severe systemic complications include disseminated intravascular coagulopathy and acute compartment syndrome from swelling muscle and reduced macrocirculation and microcirculation of injured limbs. Extracted fluid from the circulation into the swollen muscle groups may lead to hypotension and shock [67, 68].

Treatment

There are no randomized, controlled trials in the treatment of rhabdomyolysis that offer definitive guidance for treatment. Only a few interventional clinical trials in rhabdomyolysis have been reported in the past decade. There are even less data for treatment guidelines studying rhabdomyolysis management in the poisoned patient. Most recommendations are based on retrospective observational studies with small numbers of patients, animal models, case reports or series, and opinion. As with other disease states, management guidelines for the poisoned patient are often extrapolated from the care of nonpoisoned patients. The lack of high-quality evidence must be acknowledged and considered when reviewing recommendations for interventions [68].

The treatment of rhabdomyolysis involves several components in the poisoned patient (Table 3). The cornerstone of treatment centers on the prevention of acute kidney injury. No single marker or predictive model has been able to reliably assess the risk of acute kidney injury, especially in the poisoned patient.

Table 3 Components in the treatment of rhabdomyolysis in the toxicology patient (Adapted from Zimmerman and Shen [68])

Discontinuation of offending agent causing skeletal muscle injury
Control of sympathomimetic features and/or seizures
Extracellular fluid expansion (Maintain good urine output, stable hemodynamics)
Rapid identification of potentially life-threatening complications
Avoid agents that impair renal blood flow autoregulation (NSAIDs, ACE inhibitors, ARBs)

There is complete agreement that early and aggressive volume resuscitation, sufficient to restore adequate renal perfusion and increase urine flow, is the standard of care in preventing acute kidney injury in patients with rhabdomyolysis (Level II-2 recommendation) [2, 68–73]. In animals with rhabdomyolysis that had a low urinary pH, dehydration predisposed to renal injury, which was prevented with urinary dilution [55, 66, 74]. In addition, hypovolemia may occur as a result of movement of fluid into the traumatized muscle and/or to hyperthermia.

The type of fluid and the total volume of fluid remain matters of opinion. A target of 6–12 L within 24 h is a reasonable goal, as long as complications from volume overload can be avoided [68]. Strict observance of adequate urine output should be instituted with a goal rate of 2 mL/kg body weight/h [72]. Although there are no standard protocols in the literature for the duration of fluid administration, intravenous fluids should be continued until the level of creatinine kinase in the plasma decreases to less than 1000 U/L (17 *u*kat/L) or until the development of oliguric acute kidney injury limits further fluid administration [68, 71].

Although research is limited, isotonic saline is preferred because it is readily available and does not contain potassium [68]. A prospective, randomized trial compared the effects of lactated Ringer's versus 0.9% saline administered at 400 mL/h in patients with mild rhabdomyolysis

secondary to doxylamine [75]. At the end of 12 h of infusion, the serum and urine pH were higher in the lactated Ringer's group; however, the clinical significance of this outcome is unclear.

Administering bicarbonate solution to prevent rhabdomyolysis-induced acute kidney injury is a consideration but evidence of a clinical benefit is lacking (Class II-2 recommendation). Clinical reports [76] suggest that alkaline diuresis may be effective in preventing acute renal insufficiency, but there are no prospective randomized studies to support this. The concept of urinary alkalinization derives from the known precipitation of myoglobin in an acidic environment, and therefore urinary alkalinization (pH <6.5) theoretically can decrease the deposition of myoglobin in renal tubules. Alkalinization of the urine may be difficult to achieve without causing a systemic metabolic alkalosis. Conversely, some bicarbonate-containing fluids may be helpful if 0.9% saline administration results in a dilutional metabolic acidosis [68]. A current consensus statement suggests that sodium bicarbonate administration is not necessary and not superior to normal saline diuresis in increasing urine pH [77].

The use of mannitol to promote urine output and prevent acute kidney injury has also appeared in practice and the literature. However, there is even less convincing evidence for mannitol administration (Class III Recommendation). Mannitol has not been evaluated in the poisoned patient as a sole intervention in a controlled trial of rhabdomyolysis. The same small retrospective studies of bicarbonate administered with mannitol in rhabdomyolysis are cited to suggest treatment success with mannitol [78, 79]. Although many mechanisms have been postulated regarding the renoprotective effects of mannitol, prevention of heme protein trapping by diuretic action explains most of the data [63, 80]. A variety of dosing regimens using intermittent bolus and continuous infusion of mannitol are reported. Routine use of mannitol is not recommended for rhabdomyolysis, and it should not be administered to hypovolemic or anuric patients [68].

Similar to mannitol, the use of loop diuretics in the routine management of rhabdomyolysis is not recommended (Class III recommendation). Diuretics have been advocated to "convert" oliguria or anuria to nonoliguria but with very limited published experience. Care must be taken not to exacerbate hypokalemia or hypocalcemia if loop diuretics are used; conversely, use may be beneficial to treat hyperkalemia before renal recovery or hemodialysis [68].

Renal replacement therapies remain a mainstay of treatment in patients that develop rhabdomyolysis-associated acute kidney injury (Class II-1). Hemodialysis and continuous kidney replacement methods have been investigated in several studies [81–83]. The initiation of renal replacement therapy in clinical practice should not be managed by the myoglobin or creatinine kinase serum concentration but by the status of renal impairment, with complications such as life-threatening hyperkalemia, hypercalcemia, hyperazotemia, anuria, or volume overload without response to diuretic therapy [56, 77, 80]. Myoglobin has a molecular mass of 17 kDa and is poorly removed from circulation using conventional extracorporeal techniques. Therefore, intermittent hemodialysis is mostly mandated by renal or metabolic indications or drug/toxin removal. Preventive extracorporeal elimination is not routinely indicated [56].

Electrolyte disturbances that occur in the setting of rhabdomyolysis should be treated in a standard fashion. Be aware that hyperkalemia may occur within a few hours of onset of rhabdomyolysis and may be severe enough to require intervention [72]. Hyperphosphatemia may require administration of phosphate binders and treatment is dictated by the degree of phosphate elevation. In addition, hypocalcemia may occur early in the clinical course of rhabdomyolysis [66]. However, calcium should not be administered unless hyperkalemia or ventricular dysfunction occurs since calcium infusion may increase deposition of calcium in injured muscle. Hypercalcemia seen during the diuretic phase of acute kidney injury is usually self-limited and requires only conservative treatment and fluid replacement [84].

Prognosis

Outcomes from rhabdomyolysis in the poisoned patient are not known. Considering all causes of rhabdomyolysis, most patients with acute renal failure from rhabdomyolysis recover function within a few months [68]. It is reasonable to extrapolate that mortality of patients with rhabdomyolysis and acute renal failure is likely higher than in patients with no renal failure [78].

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