Drug-induced rhabdomyolysis

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Purpose of review

Drug-induced rhabdomyolysis is a common syndrome that is complex and potentially life threatening. This article reviews the pathophysiology, clinical presentations, and common compounds that cause drug-induced rhabdomyolysis.

Recent findings

The list of drugs and inciting agents that cause rhabdomyolysis is quite extensive. Rhabdomyolysis is defined as skeletal muscle injury that leads to the lysis of muscle cells and the leakage of myocyte contents into the extracellular compartments. The presenting clinical features are myalgias, myoglobinuria, and an elevated serum creatine kinase. There have been several case reports in the literature involving some common pediatric drugs that are associated with rhabdomyolysis. Diphenhydramine, Ecstasy, and baclofen have recently been implicated as the etiology of drug-induced rhabdomyolysis in several pediatric patients. Alkalinization of the urine is a controversial treatment of drug-induced rhabdomyolysis and has proven to be beneficial in some patients.

Summary

A high index of suspicion, early recognition, and adequate treatment will result in an excellent prognosis of drug-induced rhabdomyolysis.

Keywords

rhabdomyolysis, acute renal failure, myoglobinuria, creatine kinase

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Abbreviation

CK creatine kinase

1040-8703

Introduction

Rhabdomyolysis is a syndrome in which skeletal muscle disintegration results in the release of large quantities of toxic muscle cell components into the plasma. The etiology of skeletal muscle injury is quite diverse, including excessive muscular stress and ischemia, genetic defects, and direct toxic or physical damage [1]. In the past, the more common causes of acute rhabdomyolysis were from crush injuries during wartime and natural disasters [2]. More recently, as noted in one published series, drugs and alcohol have become frequent causative agents in up to 81% of cases of rhabdomyolysis [3]. Drug-induced rhabdomyolysis can be divided into a primary or a secondary myotoxic effect [1]. Primary toxic-induced rhabdomyolysis is caused by a direct insult on the skeletal myocyte function and integrity. Secondary effects of toxins are due to predisposing risk factors such as local muscle compression in coma, prolonged seizures, trauma, and metabolic abnormalities [3]. The clinical features of rhabdomyolysis range from muscle weakness to fulminant life-threatening acute renal failure. The classic triad of presenting symptoms is skeletal muscle injury, pigmented urine, and some aspect of renal dysfunction [4]. However, in drug-induced rhabdomyolysis, a subclinical presentation without these common features may be overlooked, due to other presenting symptoms that may predominate the clinical findings [5].

Physiologic mechanisms

Rhabdomyolysis is defined as a clinical and biochemical syndrome in which leakage of intracellular myocyte contents are released into the extracellular fluid and circulation [2,6]. Myoglobin is a protein that functions as an important oxygen carrier that maintains the ability of red muscles to consume oxygen [6]. The normal level of myoglobin in serum is 3 to 80 μg/L [1]. The serum level of myoglobin is dependent upon the glomerular filtration rate. When 100 g of muscle tissue has been injured, the serum proteins reach the saturation level [7]. All myoglobin above 230 mg/L is filtered through the glomerulus [5]. The presence of myoglobin in the urine will produce a dark red-brown pigmentation if the level exceeds 1 g/L [6]. At or below a pH of 5.6, myoglobin dissociates into ferrihemate and globulin [1]. Ferrihemate causes a direct deterioration of renal function, impairment of renal tubular transport mechanisms, and cell death [3]. Myoglobinuric renal failure may be explained by a direct nephrotoxicity due to ferrihemate, tubular obstruction by precipitation of myoglobin casts, and alterations in glomerular filtration rate. Myoglobin can be detected in the urine in levels as low as 5 to 10 mg/L with a dipstick

method that uses the orthotolidine reaction. Hemoglobinuria may also cause a positive orthotolidine reaction; however, the plasma will be pink, and red blood cells will be present on the microscopic evaluation. Myoglobinuria may precede and resolve prior to an increase in creatine kinase (CK) due to a short half-life of 1 to 3 hours. Therefore, a negative orthotolidine reaction does not rule out rhabdomyolysis [5].

Human tissues are composed of three different CK isoenzymes. The predominant isoenzyme is skeletal muscle and cardiac tissue is CK-MM [6]. The function of CK is to convert myocyte creatine phosphate into high-energy phosphate groups (adenosine triphosphate) used in energy requiring reactions. The release of CK into the serum may reach levels up into the hundreds of thousands [5]. Degradation of approximately 200 g of muscle can cause an increase in serum CK. Therefore, total serum CK is the most sensitive biochemical indicator of rhabdomyolysis. Serum concentration begins to increase 2 to 12 hours after the initial muscle injury and will peak at 3 to 5 days [6]. Thus it is possible for myoglobinuria to be resolved prior to an elevated serum CK. Therefore, it is important to remember that in the initial acute rhabdomyolysis syndrome, serum CK may be normal.

When massive myocyte breakdown of cell membranes occurs, other intracellular constituents are released besides myoglobin and CK. A substantial amount of fluid can accumulate within the affected muscles causing elevated pressures in the fascial compartments [2,5]. Intracellular potassium is released that can cause a significant hyperkalemia. Approximately 150 g of muscle necrosis will release more than 15 mmol of potassium. The resulting hyperkalemia may increase the risk for cardiac arrhythmias and complicate an existing acute renal failure. In the beginning phases of rhabdomyolysis, calcium accumulates within the muscle with a resulting hypocalcemia. During the later stages, calcium is mobilized from the necrotic muscle tissue and results in hypercalcemia. Release of phosphate further contributes to the hypocalcemia by forming a calcium phosphate product that is deposited in the muscle tissue [6]. Other metabolic abnormalities include metabolic acidosis, hyperuricemia, elevated lactate dehydrogenase, aldolase, creatinine, uric acid, urea, and amino transferases [7,6].

Drug-induced toxic effects

Drug-induced rhabdomyolysis can occur by a primary direct toxic effect on the myocyte function or by an indirect secondary effect that predisposes the myocyte to develop injury [1]. There are more than 150 medications and toxins that have been implicated as the etiology of skeletal muscle injury [9•]. Table 1 lists some of the more common medications that cause rhabdomyolysis. Some of the proposed direct mechanisms by which these medications alter myocyte function are inhibition of calcium metabolism by the sarcoplasmic reticulum, impairment of the production of adenosine triphosphate causing disruption of cell membranes, and alterations in carbohydrate metabolism [3]. The secondary mechanisms include drug-induced coma causing prolonged immobilization and muscle compression, seizures, and myoclonus causing increased oxygen demands on skeletal muscle tissue [1,3]. Trauma from drug-induced altered mental status, agitation, and delirium can cause tissue ischemia and crush injury [1].

Many of the common drugs of abuse have been reported to cause rhabdomyolysis. One report estimated that approximately 20% of all cases of myoglobinuria due to rhabdomyolysis were the result of alcohol ingestion [5]. Ethanol-induced rhabdomyolysis may develop from direct toxic effects on the sarcoplasmic reticulum by increasing sodium permeability and disrupting calcium homeostasis, disintegration of the cell membrane, and alterations in intracellular energy sources [9•,10]. The secondary effects of alcohol pertain to the altered mental status, loss of consciousness, and coma that can lead to prolonged immobilization and muscle compression [9•]. Ethanol ingestions can present with a history of poor nutrition, hypokalemia, and hypophosphatemia, which can predispose the patient to rhabdomyolysis [9•].

Table 1. Selected drugs that cause rhabdomyolysis

Acetaminophen	Caffeine	Hydrocarbons	Methamphetamine	Strychnine
Amoxapine	Carbone Monoxide	Hydrocortisone	Methanol	Succinylcholine
Amphetamines	Chloral hydrate	Hydroxyzine	Mineralocorticoids	Sympathomimetics
Amphotericin B	Chlorpromazine	Inhalation anesthetics	Morphine	Theophylline
Anticholinergics	Cocaine	Isoniazid	Narcotics	Trimethoprim-sulfamethoxazole
Antidepressants	Dexamethasone	Isopropyl Alcohol	Neuroleptics	Vasopressin
Antihistamines	Diazepam	Ketamine Hydrochloride	Phencyclidine	
Antipsychotics	Diuretics	Licorice	Phenobarbital	
Baclofen	Ecstasy	Lithium	Phenothiazines	
Barbiturates	Ethanol	Lorazepam	Phenytoin	
Benzodiazepines	Fluoroacetate	Lysergic acid diethylamide	Prednisone	
Betamethasone	Glutethimide	Loxapine	Salicylate	
Butyrophenones	Heroin	Marijuana	Serotonin antagonists	

Cocaine, another common drug of abuse, can cause a direct effect on the muscle tissue, inducing vasoconstriction and tissue ischemia [4]. Cocaine has also been shown to cause leakage of CK from skeletal muscle myocytes [11]. Cocaine-associated rhabdomyolysis may also be contributed to the state of hyperthermia and hyperactivity, which increases energy requirements and depletes the energy resources [5]. When the body's thermoregulatory mechanisms of heat production and dissipation fail, the myocyte cannot maintain its function and is destroyed [12•]. There are several other drugs that induce injury by this hypermetabolic mechanism, including inhalation anesthetics, sympathomimetics, serotonin antagonists, antipsychotics, and anticholinergics [12•].

Ketamine hydrochloride is an analogue of phencyclidine and is used as a dissociative anesthetic for procedural sedation. It can also be ingested, inhaled, or injected as a drug of abuse. In a case series of 20 patients ages 15 to 40 years, two developed rhabdomyolysis, both of which required benzodiazepine sedation for combativeness [13]. Ketamine hydrochloride, as well as phencyclidine, can produce agitation and prolonged muscular activity that may contribute to muscle damage. However, phencyclidine may be more likely to cause rhabdomyolysis due to seizures, hyperthermia, and delirium requiring restraints that can predispose to muscle tissue injury [13].

Methamphetamine, a drug of abuse and another stimulant, was implicated as the most common cause of rhabdomyolysis in a review of 18 pediatric patients who had inadvertently ingested the drug [14]. Ecstasy was also reported by Hinkelbein *et al.* to cause fulminant rhabdomyolysis in a 16-year-old female who took 30 tablets in a suicide attempt [15•]. Ecstasy is 3,4-methylenedeoxymethamphetamine (MDMA), which is an analog of amphetamine. One the most life-threatening complications of Ecstasy overdose is hyperthermia. In one case report by Walubo and Seger, a 53-year-old man died of multiorgan failure and rhabdomyolysis after consuming an unknown amount of Ecstasy. Ecstasy releases serotonin into the brain, which stimulates sympathetic mechanisms to increase catecholamines. Muscular hyperactivity and severe hyperthermia result from release of calcium from the sarcoplasmic reticulum and increased metabolic demands [16]. Other medications that can cause prolonged muscular contractions such as choreoathetosis or dystonic reactions are phenothiazines and butyrophenones [5]. Prolonged seizure activity, which can cause rhabdomyolysis, can be induced by isoniazid, strychnine, amoxapine, loxapine, theophylline, lithium, and withdrawal from sedative hypnotics or ethanol [5].

Caffeine is a common drug that is usually not implicated in acute ingestions from overdose. However, there is a case report of a previously healthy 21-year-old male who ingested 10 magnum 357s (an over-the-counter stimulant that contains 357 mg of caffeine) [17]. He presented initially with nausea, vomiting, and muscle twitching. On day 5, he presented with decreased urine output and persistence of symptoms. At this time, his CK was 1134 U/L, and a urinalysis revealed proteinuria but no myoglobinuria. His blood urea nitrogen was 18 mg/dl and creatinine 16 mg/dl. Caffeine interferes with calcium transport by the sarcoplasmic reticulum resulting in accumulation of calcium within the cell. This can potentiate muscle contraction and increase the energy demands that may cause cell destruction. Therefore, this patient's rhabdomyolysis was most likely due to direct toxic effects that caused increased muscular activity and myocyte injury [17].

Acetaminophen is a common agent used in pediatrics as an antipyretic and an analgesic. It is well known that acetaminophen overdoses cause severe hepatic injury. However, in one report of an overdose by a 44-year-old female, not only did hepatotoxicity occur, but rhabdomyolysis, hypothermia, hyperglycemia, and acute renal failure. Therefore, acetaminophen should be added to the list of drugs that cause direct toxic effects on myocytes as well as hepatocytes [18].

Drugs that induce central nervous system depression can cause prolonged immobilization, muscle compression, and tissue ischemia that results in myocyte injury. Compounds such as narcotics, benzodiazepines, cyclic antidepressants, antihistamines, ethanol, glutethimide, and barbiturates all cause an altered level of consciousness and may predispose to the development of rhabdomyolysis [5]. Carbon monoxide poisoning may enable a patient unconscious for a prolonged period of time, predisposing to the development of rhabdomyolysis. Carbon monoxide can cause a functional anemia that impedes oxygen delivery to tissues [5]. Carbon monoxide also impairs adenosine triphosphate production, causing a direct effect on myocyte energy production. Other agents such as cyanide and hydrogen sulfide can inhibit electron transport and disrupt adenosine triphosphate production [5].

There are many other drugs that induce rhabdomyolysis through other mechanisms. Hypokalemia caused be diuretics, mineralocorticoids, licorice, and amphotericin B can predispose to rhabdomyolysis [5]. Corticosteroids appear to have a direct toxic effect on skeletal muscle, as seen in severe asthmatics who develop rhabdomyolysis. Acute hypersensitivity reactions producing rhabdomyolysis have been reported with phenytoin and trimethoprim-sulfamethoxazole [5]. Cholesterol-lowering agents like HMG CoA reductase inhibitors have a direct effect on the skeletal muscle tissue. Succinylcholine can

cause myoglobinuria in the absence of the hereditary disorder of malignant hyperthermia, especially in children [5].

Neuroleptic malignant syndrome is characterized by the gradual development of hyperthermia, muscle rigidity, autonomic instability, altered mental status, myoglobin, and elevated serum CK. Drugs that cause neuroleptic malignant syndrome include phenothiazines, butyrophenones, antipsychotics, narcotics, and antidepressants [6].

Intrathecal baclofen infusion is used for children with cerebral palsy to treat spasticity and dystonia. As reported in the case of a 9-year-old boy with cerebral palsy during an accidental withdrawal, multisystem organ failure and rhabdomyolysis developed when his catheter became disconnected from the pump. The muscle injury that caused the rhabdomyolysis may have been due to hypertonicity, prolonged seizures, and hyperthermia. His presentation was similar to neuroleptic malignant syndrome [19].

Case report

Stucka *et al.* reported the case of a previously healthy 23-month-old boy who ingested an unknown amount of 50 mg diphenhydramine capsules. The patient presented 4 hours after ingesting the capsules. He presented with tachycardia, fixed and dilated pupils, erythematous dry skin, and agitation. He did not require physical restraints. Significant lab values were carbon dioxide 17 mmol/L, anion gap 11, and potassium 4.9 mmol/L. Blood urea nitrogen and creatinine were within normal limits. Initial CK was 1619 U/L with a normal urinalysis. Repeat CK 9 hours later was 4505 U/L with a normal urinalysis. A serum diphenhydramine level of 136 ng/ml (normal range 30–50 ng/ml) was obtained 34 hours after the ingestion. The patient improved with intravenous fluids plus sodium bicarbonate, and the last CK was 1205 U/L on day 4. His renal function remained normal [8•].

Diphenhydramine is a commonly prescribed pediatric drug used for allergic reactions, sedation, and sleep induction. It is an over-the-counter H1-histamine receptor antagonist. There have been reports of rhabdomyolysis following diphenhydramine overdoses in adults that were associated with seizures, shock, hyperthermia, coingestants, prolonged immobilization, and other contributing risk factors. However, this patient is a child and had no confounding risk factors for rhabdomyolysis. This case suggests the direct effect of diphenhydramine on myocytes [8•].

Clinical presentations

Rhabdomyolysis may present with a wide variety of clinical symptoms from mild myalgias to severe acute renal failure. Muscles may be tender, stiff, or weak [6]. However, most patients with drug-induced rhabdomyolysis do not complain of swelling or tenderness over the involved muscle at the time of admission. They may develop a "second wave phenomenon" in which a delayed increase in fascial compartment pressure causes compression neuropathies, swelling, and tenderness. Compartment syndromes in drug-induced rhabdomyolysis usually occur secondary to prolonged immobilization or coma, which can result in contractures and amputations [5]. Treatment includes immediate surgical fasciotomy to release the increased compartmental pressures. Acute renal failure is complicated by hypovolemia, cast formation, renal vasoconstriction, and ferrihemate toxicity. Replacing circulating blood volume and maintaining urine output is essential for prevention of acute tubular necrosis [6]. Disseminated intravascular coagulation can be significant in patients with rhabdomyolysis. Thromboplastin and plasminogen activator are released from the injured myocyte and cause fibrinolysis. Acute cardiomyopathy can present from direct toxic effects of drugs on the cardiac muscle. Respiratory failure can result from involvement of respiratory muscles during rhabdomyolysis [5].

Treatments

In any acute life-threatening ingestion or illness, the airway, ventilation, and perfusion should be the initial priority. Thereafter, the goal of treatment of rhabdomyolysis is to cease muscle destruction. Table 2 refers to the appropriate treatments for patients who are symptomatic from drug-induced rhabdomyolysis. The prevention of increased agitation, seizures, and abnormal movements must be attempted with pharmacologic agents. Treatment of hyperthermia is essential using external cooling measures and controlling for muscular hyperactivity with benzodiazepines. Electrolyte abnormalities that must be corrected are hyponatremia, hypernatremia, hyperglycemia, hypocalcemia, and decreased phosphorous. If compartment syndrome is present, the compartment pressures should be measured. If compartmental pressures are over 30 to 50 mmHg, a fasciotomy must be considered. Alkalinization of urine and mannitol has shown to be effective in some patients with acute renal failure. However, there is no standard protocol in the literature, and the bicarbonate may potentiate an already existing hypocalcemia [9•]. In the case of drug-induced rhabdomyolysis, eliminating the exposure of the toxic agent may be the only treatment.

Table 2. Treatment of drug-induced rhabdomyolysis

Elimination of exposure
Sedation
External cooling
Hydration
Alkalinization
Correction of electrolyte abnormalities

Conclusion

The etiologies of rhabdomyolysis are extremely diverse and multifactorial. Drug- and toxin-induced rhabdomyolysis is a common and potentially deadly syndrome that is often unrecognized. This category of rhabdomyolysis is complicated by the fact that there are primary and secondary mechanisms of muscle cell injury. There are a multitude of compounds that can cause rhabdomyolysis. The presenting symptoms may be discrete and misleading. Therefore, careful history and physical are important to obtain to determine the cause of symptoms, specifically in ingestions. With early recognition and a high index of suspicion, most patients with rhabdomyolysis will have an excellent prognosis. All patients who appear symptomatic from toxic ingestions should be suspected of having rhabdomyolysis.

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