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AN OVERVIEW OF DRUG INDUCED RHABDOMYOLYSIS

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ABSTRACT

Drug induced rhabdomyolysis is one of the potentially lethal condition in which there is disintegration of the skeletal muscles with subsequent release of their contents into the circulation and extracellular fluid. There are multiple causes for rhabdomyolysis that include compression injuries, convulsions, electrocution, drugs, toxins, metabolic derangements, endocrinal disorders, massive blood transfusions and inherited myopathies. Here we have made an attempt to review the drugs that cause rhabdomyolysis along with its mechanisms, clinical presentation and management.

Key Words: Drugs, Rhabdomyolysis, Myoglobinuria.

INTRODUCTION

Rhabdomyolysis is a clinical syndrome characterized by classical triad of myalgia, weakness and myoglobinuria (Phillips D *et al.*, 2012). There will also be an associated worsening of renal function caused by skeletal muscle injury and results in release of intracellular contents into the extracellular fluid. Diagnosis is usually made by measuring these released substances in either plasma or urine. Injury can be reversible or irreversible, potentially leading to significant morbidity including renal failure and death (Bontempo LJ *et al.*, 2006). Clinically, rhabdomyolysis is characterized by muscle necrosis and the release of intracellular muscle constituents into the circulation. Creatine kinase (CK) levels are markedly elevated along with muscle pain, metabolic acidosis and myoglobinuria (Adams JG *et al.*, 2008). The severity of illness ranges from asymptomatic elevations in serum muscle enzymes to life-threatening disease associated with extreme enzyme elevations, dyselectrolytemia and acute kidney injury.

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Pathophysiology

Mechanism of drug induced rhabdomyolysis is not understood completely as all the reports are solely due to drug induced is questionable. Drugs taken in overdose are complicated by attendant circumstances which cause or contribute to acute muscle necrosis which include hypokalemia, seizures, hypothermia, trauma, metabolic acidosis, hypoxia and prolonged coma with immobilization, muscle compression and/or occlusion of the regional blood supply (Penn AS *et al.*, 1972).

The clinical manifestations and complications of rhabdomyolysis result from muscle cell death, which may be triggered by a variety of initiating events. The final common pathway for injury is an increase in intracellular free ionized cytoplasmic and mitochondrial calcium which may be caused by depletion of adenosine triphosphate (ATP). The increased intracellular calcium leads to activation of proteases, increased skeletal muscle cell contractility, mitochondrial dysfunction and the production of reactive oxygen species resulting in skeletal muscle cell death. ATP depletion causes dysfunction of the Na/K-ATPase and Ca^{2+} ATPase pumps that are essential to maintaining the integrity of the myocyte. Depletion of ATP depletion also causes myocyte injury and the release of

intracellular muscle constituents, including creatine kinase (CK) & other muscle enzymes, myoglobin and various electrolytes.

Causes

There are large number of potential causes of rhabdomyolysis which can be broadly divided into three categories, that includes 1.Traumatic or muscle compression (eg, crush syndrome or prolonged immobilization); 2. Nontraumatic exertional (eg, marked exertion in untrained individuals, hyperthermia, or metabolic myopathies); 3. Nontraumatic nonexertional (eg, drugs or toxins, infections or electrolyte disorders). Drugs that cause rhabdomyolysis are summarized in Table 1.

Diagnosis and Management

Rhabdomyolysis is not an uncommon event of rapid destruction of skeletal muscle cells. The range of trigger mechanisms is wide and span from mechanical injury, ischemia, infections, genetic alterations to drugs and toxins. Regardless of the underlying etiology, muscle injury triggers a cascade of events leading to increased intracellular calcium, cellular hypoxia, and depletion of muscle cell adenosine triphosphate (ATP) with consequent cell membrane injury and release of cellular constituents into the circulation.

Potassium, phosphate, myoglobin, creatine kinase are among the released constituents; of these, myoglobin plays a key role in the pathogenesis of rhabdomyolysis. When large amount of myoglobin is released, the plasma binding capacity is exceeded and free extraneous myoglobin is filtered through the glomeruli and deposited in the renal tubules, causing tubular obstruction and renal damage.

The spectrum of potential complications following acute rhabdomyolysis comprises hyperkalaemia, a rapidly rising serum creatinine, hyperuricaemia, hypo as well as hypercalcaemia, hyperphosphataemia, disseminated intravascular coagulation (DIC), metabolic acidosis, cardiomyopathy and respiratory failure etc. Death is thought to arise from acute metabolic disturbances but the prognosis of renal, muscular and neurological dysfunction is good (Koppel C *et al.*, 1989).

The most sensitive indicator of rhabdomyolysis is creatine phosphokinase (CPK), an enzyme that catalyzes the transportation of phosphate to generate ATP. It is the CPK-MM isoform which is elevated. The half life of CPK is approximately 1.5 days; thus during the first 12 hours of the onset of rhabdomyolysis, CPK starts rising, reaching a peak within the first 72 hours and the baseline level within the next 3 to 5 days. In contrast, the half-life of myoglobin is relatively short, being 1 to 3 hours. The level of myoglobin in serum increases within 1 to 3 hours of onset of rhabdomyolysis, peaks within 8-12 hours, and returns to baseline within 24 hours.

Mainstay treatment for rhabdomyolysis include airway protection, volume resuscitation, and correction of metabolic derangements. Maintenance of urine output (200 ml/hr or greater) should be achieved with volume resuscitation in the form of intravenous normal saline, as this particular isotonic crystalloid does not contribute significantly to hyperphosphatemia. Continuous renal replacement therapy or hemodialysis is usually the definitive treatment modalities in these patients.

Diuretics should be cautiously used and central venous pressure monitoring should be in place to assess intravascular volume status. An osmotic diuretic such as mannitol is the agent of choice in rhabdomyolysis. It is safer to avoid loop diuretics such as furosemide, as this can contribute to urine acidification and tubular cast formation. The efficacy of urine alkalinization remains controversial. Myoglobin protein binding and subsequent cast precipitation is enhanced in acidic conditions. Urine alkalinization could theoretically enhance renal myoglobin clearance by increasing myoglobin's solubility. Sodium bicarbonate could aid in this management goal. Patients with rhabdomyolysis who have been severely injured or who are profoundly hypotensive tend to be acidotic and may benefit from supplemental sodium bicarbonate (Adams JG *et al*., 2008).

Hyperkalemia is the most dangerous electrolyte disturbance in patients with rhabdomyolysis because of its propensity to precipitate lethal cardiac arrhythmias, as well as diminish contractility. Continuous cardiac monitoring should be in place and hyperkalemia should be treated aggressively.

Table 1. Drugs that cause rhabdomyolysis (in alphabetical order)

Acetaminophen	Diuretics	Morphine
Amoxapine	Dexamethasone	Neuroleptics
Amphetamines	Ethanol	Narcotics
Anticholinergics	Flouroquinolones	Strychnine
Antidepressants	Heroin	Succinylcholine
Antihistamines	Isoniazid	Sympathomimetics
Alcohol	Isopropyl Alcohol	Theophylline
Antipsychotics	Lithium	Trimethoprim-sulfamethoxazole
Benzodiazepines	Licorice	Vasopressin
Barbiturates	Lorazepam	Phenothiazines
Betamethasone	Lysergic acid	Phenytoin

Chloral hydrate	Loxapine	Prednisone
Chlorpromazine	Methanol	Serotonin antagonists
Cocaine	Mineralocorticoids	Salicylate
Cytotoxic drugs	Metals	Valproate

CONCLUSION

Drug induced rhabdomyolysis is often an unrecognized entity that occurs most commonly in drug overdosage. It should be looked for in severely poisoned patients and treated aggressively. Fortunately the diagnosis of rhabdomyolysis requires only a few laboratory tests accompanied by the clinical presentation and also detailed drug history. Targeting the syndrome as opposed to merely treating symptoms can significantly reduce morbidity and mortality in patients with rhabdomyolysis.

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