Drug-induced myopathies

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Originally released June 22, 1998; last updated June 24, 2016; expires June 24, 2019

Introduction

This article includes discussion of drug-induced myopathies, toxic myopathy, alcohol myopathy, drug-induced myalgia, statin-induced myopathy, and steroid myopathy. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

A large number of drugs can produce myopathy. Various forms of drug-induced myopathies and the drugs that cause them are described in this article. The manifestations can range from muscle pain to rhabdomyolysis, a life-threatening condition. Widely used cholesterol-lowering drugs have been associated with myopathy. Pathomechanism, differential diagnosis, and management of various drug-induced myopathies are described in this article.

Key points

• Clinical manifestations of drug-induced myopathy are often indistinguishable from those of myopathies due to other causes.
• History of use of a drug known to induce myopathy and any specific manifestation are helpful in diagnosis.
• Myopathy usually resolves on discontinuation of the offending drug, but muscle damage may persist in some cases.
• Elevated serum creatine kinase is the most sensitive indicator of muscle damage.
• In some cases muscle biopsy may be required for definitive diagnosis of muscle pathology.

Historical note and terminology

Therapeutic drugs can produce adverse effects on the skeletal muscle, the neuromuscular apparatus, or the peripheral nerves. Alcohol, one of the oldest drugs known, has an ability to cause muscle weakness that has been recognized since the middle of 19th century. The adverse effects of pharmaceuticals on muscles have been recognized mostly within the last 50 years.

Clinical manifestations of drug-induced myopathies range from muscle pain to serious sequelae such as rhabdomyolysis. Although some categories of drugs are associated with specific forms of myopathies, a drug can cause more than 1 type of myopathy, and the term “myopathies” is used in a broad sense to report the adverse effect of drugs on the muscles. The term “myopathy” usually refers to skeletal muscle, although occasionally it is applied to cardiac muscle as “cardiac myopathy.”

History of drug use is important in the evaluation of patients presenting with various muscle disorders, and an understanding of the pathophysiology of drug-induced myopathy is useful in planning the management of these patients.

Clinical manifestations

Presentation and course

Clinical manifestations of drug-induced myopathies are shown in Table 1:

Table 1. Clinical Manifestations of Drug-Induced Myopathies

• Myalgia: muscle pain, stiffness, or cramps without neurologic signs
• Myotonia: delayed relaxation of skeletal muscle after a voluntary contraction
• Painless proximal myopathy characterized by muscle weakness
• Painful myopathies
- with drug-induced polymyositis
- without polymyositis

• Focal myopathy with focal area of damage due to injections
• Myokymia or rhythmic rippling of muscles corresponding to widespread myokymic discharges seen on EMG
• Hypokalemic myopathy associated with weakness of muscles due to drug-induced hypokalemia
  • Mitochondrial myopathy associated with inhibition of mitochondrial DNA and characterized by ragged red fibers
• Rhabdomyolysis: acute muscle necrosis with myoglobinuria and systemic complications
  • Malignant hyperthermia
• Secondary effects of myopathies
  - renal shutdown in rhabdomyolysis
  - compartment syndromes due to myositis

Clinical manifestations of drug-induced myopathy are often indistinguishable from those of myopathies due to other causes, as well as from idiopathic forms. Fatigue has been reported as the only clinical manifestation of colchicine-induced myopathy (Lo et al 2010). Some specific features are mentioned here.

**Chloroquine myopathy.** This has been seen with the use of chloroquine as both an antimalarial as well as an antirheumatic agent. There is insidious development of painless muscle weakness, particularly of proximal muscles associated with muscle wasting. There is associated cardiac muscle involvement, and the diagnosis is made by endomyocardial biopsy in addition to skeletal muscle biopsy.

**Cholesterol-lowering-agent myopathy.** Most patients with this myopathy complain of muscle cramps and weakness. Myotonia and elevated creatine kinase are also common findings, and it may proceed to rhabdomyolysis.

**Corticosteroid myopathy.** Chronic myopathy caused by corticosteroid excess, whether endogenous or exogenous, is well known and is described in the course of Cushing syndrome. Myopathy is reported in the course of various diseases treated with corticosteroids for long periods, such as systemic lupus erythematosus, rheumatoid arthritis, bronchial asthma, and polymyositis. Corticosteroids induce a painless myopathy with slow onset of proximal muscle weakness of the lower extremities and seldom of the upper extremities. Even inhaled steroids can induce proximal myopathy.

Acute myopathy may occur less often within a week after onset of treatment with high dose corticosteroids. Such myopathy, involving respiratory muscles, has been described in patients with asthma and chronic obstructive pulmonary disease. Patients with status asthmaticus treated with high-dose corticosteroids in combination with neuromuscular blockade induced by steroidal muscle relaxants are more prone to develop myopathy, which is also referred to as “blocking agent-corticosteroid” myopathy. Even without combination with neuromuscular blocking agents, high parenteral doses of corticosteroids may produce acute myopathy in patients with myasthenia gravis.

**Emetine.** Emetine is the active ingredient of ipecac (the dried root of a plant used as a syrup for expectorant, emetic, and antiamebic properties). It is available as an over-the-counter preparation. Emetine myopathy is characterized by progressive muscle weakness. Strength returns after cessation of ipecac abuse. Myopathy has been reported following the use of ipecac syrup by young women with eating disorders. Muscle biopsy findings in these patients were vacuolar degeneration and myosin of muscle fibers with a loss of sarcoplasm and small cytoplasmic bodies. Myopathy improved in these patients after cessation of ipecac abuse.

**Rhabdomyolysis.** The condition is characterized by widespread muscle pain, weakness, and dark urine. Myoglobinuria is an early feature and may lead to the following complications:
  • Hyperuricemia
  • Rapidly rising serum creatinine
  • Metabolic acidosis
  • Disseminated intravascular coagulation
  • Acute renal failure
  • Electrolyte disturbances: K, Ca, and Mg
  • Cardiomyopathy
  • Respiratory failure
  • Compartment syndromes due to swelling of muscles of extremities
Critical illness myopathy. This has been reported in critically ill patients treated with high-dose intravenous corticosteroids and nondepolarizing neuromuscular junction-blocking agents in the intensive care unit and may be 1 of the mechanisms of ICU-acquired weakness. Minimizing the use of these agents may prove helpful in preventing the occurrence of these disorders. However, comatose and critically ill patients have been reported to develop muscle weakness or paralysis (quadriplegia) during the course of sepsis and multiple organ failure where drugs such as steroids, neuromuscular-blocking agents, and aminoglycosides are not responsible for paralysis. These patients may become completely paralyzed because of nondrug-induced neuromuscular disorders.

**Prognosis and complications**

Prognosis of drug-induced myopathy is generally good and the symptoms subside after discontinuation of the offending drug. In more advanced cases of necrotic myopathy, residual muscle weakness or paralysis of the involved muscle may persist.

In zidovudine-induced mitochondrial myopathy, serum creatine kinase levels return to normal within 4 weeks of cessation of therapy and ultrastructural abnormalities also improve after discontinuation of the drug. Discontinuation of the drug therapy is not always possible in patients with AIDS. In such patients, biopsy-proven zidovudine myopathy has been reported to remain stable up to 6 months without dosage reduction or discontinuation of AZT.

Rhabdomyolysis may cause death due to acute metabolic disturbances, but prognosis for recovery of renal, muscular, and neurologic function is good if treated early. If untreated, patients with malignant hyperthermia may die within minutes of ventricular fibrillation, within hours from pulmonary edema or coagulopathy, or within days from neurologic damage or renal failure.

**Biological basis**

**Etiology and pathogenesis**

Muscle tissue is sensitive to drugs due to its high metabolic activity and potential sites for disruption of energy-producing pathways (Walsh and Amato 2005). Drugs that produce various types of myopathies are shown in Tables 2 through 8. These are based on reports of adverse drug reactions, only a small number of which are published. These reports are received by the manufacturers and submitted to the health authorities. Important adverse effects of a drug are listed in the Physicians' Desk Reference. Causal relation is not established in all cases, but suspicion is by association. Nevertheless, these tables may serve as a check list during history taking of a patient with myopathy. References are given for publications within the last decade and older references can be found in the book on drug-induced neurologic disorders (Jain 2011).

**Table 2. Drugs/Therapies Reported to Cause Myopathy**
• Alcohol
• Amiodarone*
• Anticancer agents: vincristine
• Anesthetic: intravenous propofol
• Carbimazole
• Chloroquine*
• Cholesterol-lowering agents: statins*
• Cimetidine
• Clozapine
• Colchicine*
• Corticosteroids*
• Cyclosporin
• Daptomycin (Ferrera et al 2012)
• D-penicillamine
• Emetine
• Epsilon-aminocaproic acid*
• Fluoroquinolone antibiotics: ofloxacin/levofloxacin
• Gene therapy: direct insertion of transgenes to the muscle (Dalakas 2009)
• Germanium
• Glycyrrhizin* (licorice)
• Gold salts
• Growth hormone
• Hydroxychloroquine
• Interferon-alpha-2b
• Ipecac
• Isoniazid (Chaouch et al 2011)
• Labetalol
• Minocycline (Bokuda et al 2012)
• Omeprazole
• Perhexiline
• Phenylbutazone
• Phenytoin
• Propylthiouracil
• Pyrazinamid, an antitubercular agent (Shah and Venkatesan 2015)
• Retinoids
  - etretinate
  - tretinoin
  - isotretinoin
• Telbivudine for treatment of chronic hepatitis B (Wang et al 2012)
• Tranilast
• Sulfonamide
• Zidovudine*

*Well documented. The rest are based on isolated case reports, and a causal relationship is not established.

Table 3. Drugs Reported to Cause Myalgia or Muscle Cramps
• All-trans retinoic acid
• Angiotensin-converting enzyme inhibitors
• Anticholinesterases
• Antimony compounds: sodium stibogluconate, meglumine antimonate
• Azathioprine
• Beta-adrenergic agonists
• Calcium antagonists
• Captopril
• Carbimazole, treatment of hyperthyroidism
• Cimetidine
• Clofibrate
• Colchicine
• Corticosteroids, withdrawal
• Cytotoxic drugs
• Danazol
• Dexamethasone
• Diuretics
• D-penicillamine
• Enalapril
• Filgrastim (granulocyte colony-stimulating factor)
• Gold compounds
• Isotretinoin
• Ketorolac
• Labetalol
• Levamisole
• Lithium
• Losartan potassium
• L-tryptophan
• Metolazone
• Nifedipine
• Paclitaxel
• Pindolol
• Procainamide
• Retinoids
• Rifampicin
• Salbutamol
• Suxamethonium chloride
• Terbutaline
• Teriparatide (Luigetti et al 2013)
• Zidovudine
• Zimeldine

Table 4. Fibrous Myopathy Following Intramuscular Drug Injection

• Antibiotics
• Butorphanol
• Botulinum toxin
• Chloroquine
• Chlorpromazine
• D-propoxyphene
• Drug abuse
• Meperidine
• Paraldehyde
• Pentazocine (Kolikonda et al 2015)

Table 5. Drugs that Induce or Unmask Myotonic Disorders

• Anesthetic propofol*
• Beta-agonists
  - fenoterol
  - ritodrine
• Beta-blockers
  - propanolol
• Clofibrate
• Depolarizing muscle relaxants*
• Diazacholesterol
• Diuretics*
  - furosemide
  - ethacrynic acid
  - mersalyl
  - acetazolamide
• Iodine compounds
• Vincristine

*Well documented. The rest of the list is based on isolated case reports.

Table 6. Drugs Reported to Produce Hypokalemic Myopathy
• Amphotericin B
• Carbenoxolone
• Diuretics
• Licorice
• Purgatives

Table 7. Drugs Reported to Cause Myositis
• Alcohol
• Amiodarone
• Anticancer agents: gemcitabine
• Chloroquine*
• Cimetidine
• Clevudine, an antiviral agent for hepatitis B (Yang et al 2010)
• Cocaine
• Colchicine
• Corticosteroids*
• D-Penicillamine*
• Interferon-alpha
• Interleukin-2
• Ipecac
• Ipilimumab
• Lansoprazole
• Leflunomide (Ochi et al 2009)
• Leuprolide
• Lipid-lowering agents*
  - lovastatin
  - pravastatin
• L-Tryptophan*  
• Pentazocine  
• Phenobarbital  
• Procainamide  
• Tranilast  
• Voriconazole, an antifungal agent for invasive aspergillosis (Shanmugam et al 2009)  
• Zidovudine

*Well documented. The rest of the list is based on isolated case reports.

**Table 8. Drugs Reported to Induce Rhabdomyolysis**

• Alcohol  
• Amiodarone  
• Aminocaproic acid  
• Amoxapine  
• Amphetamines  
• Amphotericin  
• Antineoplastics  
  - cytarabine  
  - cyclophosphamide  
• Anesthetics*  
• Barbiturates  
• Carbenoxolone  
• Chlorpromazine  
• Cholesterol-lowering agents*  
  - bezafibrate  
  - pravastatin  
  - lovastatin  
  - simvastatin  
  - cerivastatin
Among the listed drugs, those that most frequently induce myopathy are steroids, statins, fibrates, antiretrovirals, immunosuppressants, colchicine, amiodarone, and anticancer drugs. Some of these drugs manifest their myotoxic potential only in combination with other drugs or conditions predisposing to muscular disorders.

Based on pathomechanisms, 6 main categories of toxic myopathies are recognized: (1) necrotizing myopathy; (2) vacuolar myopathy; (3) inflammatory myopathy; (4) mitochondrial myopathy; (5) steroid myopathy; and (6) hypokalemic myopathy. Some of these overlap with the clinical types. Correlation of structural lesions in muscles and clinical manifestations is usually not possible, but an attempt has been made by as shown in Table 9.

Table 9. Correlation of Structural Lesions and Clinical Manifestations in Drug-Induced Myopathies

<table>
<thead>
<tr>
<th>Toxic effects on muscle structure</th>
<th>Principal clinical manifestation</th>
<th>Examples or drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle fiber necrosis; damage to intracytoplasmic membrane</td>
<td>Painless proximal muscle weakness</td>
<td>Chloroquine</td>
</tr>
</tbody>
</table>
• Muscle fiber necrosis and sarcolemmal damage
  Muscle pain and swelling; proximal muscle weakness, elevated CK, myoglobinuria
  Clofibrate

• Myofibrillary damage
  Proximal muscle weakness with decrease of muscle contractility
  Emetine

• Type 2 fiber atrophy
  Chronic proximal muscle weakness
  Cortisone

**Toxic effects on muscle function**

<table>
<thead>
<tr>
<th>Contractility</th>
<th>Genetic predisposition; increased CK; hyperthermia; muscle weakness and pain; neuroleptic malignant syndrome</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Inhalation anesthetics</td>
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<table>
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<tr>
<th>Energy metabolism (mitochondrial myopathy)</th>
<th>Muscle weakness, muscle pain on exertion</th>
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<tr>
<td></td>
<td>Zidovudine</td>
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**Pathophysiology of drug-induced myopathies.** These myopathies are mostly due to the toxic effect of the drugs on the muscles as a primary event, as evidenced by elevation of serum creatine kinase. There is also excessive neural driving or accumulation of acetylcholine at the neuromuscular junction by cholinesterase inhibitors such as phencyclidine. Finally, other drug-induced disturbances may produce myopathies as a secondary event.

**Direct effect of drugs on muscle.** These are as follows:

- Effect on the muscle plasma membrane, which is the most exposed part of the muscle and is vulnerable to toxins. Disturbances of ionic permeability of the membrane increase entry of calcium into the cell, leading to myofibrillar contracture and initiating a chain of events that lead to cell death. Drug-induced changes in electrical properties of muscle plasma membrane can produce myalgia, cramps, and myotonia. Uncoupling of oxidative phosphorylation can produce mitochondrial myopathy. Propofol infusion syndrome of metabolic acidosis, acute cardiomyopathy, and skeletal myopathy is caused by the failure of free fatty acid metabolism due to inhibition of free fatty acid entry into the mitochondria and also specific sites in the mitochondrial respiratory chain.

- Interference with protein synthesis and degradation in muscles. Emetine can inhibit protein synthesis and mitochondrial respiration, leading to disruption of cell membrane if high concentrations of drugs are present.

- Autophagic degeneration and phospholipid accumulation in muscles (e.g., chloroquine-induced myopathy). There may be disruption of the microtubule-dependent cytoskeletal network that interacts with lysozymes, as in the case of colchicine-induced myopathy.

- Infiltration of muscles with neutrophils (e.g., as an effect of drugs such as granulocyte colony-stimulating factor).

**Indirect effects of drugs on muscle.** These are due to other drug-induced disorders as follows:

- Electrolyte disturbances such as in hypokalemia and hyponatremia
- Drug-induced immune disturbances leading to myositis
- Drug-induced metabolic disorders (e.g., carnitine deficiency associated with pivampicillin).

**Pathomechanism of drug-induced myalgia.** Drug-induced muscle pain may be due to the following mechanisms:

**Mechanical pain.** This pain may be due to mechanical displacement of the muscle by a hematoma, a spasm, or rigidity, or secondary to a drug-induced movement disorder.

**Inflammatory pain.** This pain may be due to myositis or rhabdomyolysis.

**Ischemic pain.** This pain may be due to drug-induced spasm or vasculitis involving the peripheral arteries.

**Enhanced prostaglandin synthesis.** Drugs that enhance prostaglandin synthesis may cause muscle pain. This pain is usually relieved by prostaglandin inhibitors such as piroxicam.
Decrease in serum calcium with influx into muscle cells. This mechanism has been proposed for suxamethonium-induced myalgia. High intracellular calcium ion concentration may cause damage to muscle spindles by asynchronous muscle bundle contractions.

Referred pain. This pain may occur with drug-induced peripheral neuropathies.

Pathomechanism of drug-induced myositis. Myositis is generally considered to be an idiopathic inflammatory disorder of the muscle. Environmental agents acting on genetically susceptible persons lead to physiologic responses involving immune activation and subsequent tissue damage, which are recognized as myositic syndromes. Persons receiving the antirheumatic drug D-penicillamine can develop a syndrome that is clinically, pathologically, and serologically indistinguishable from polymyositis. The syndrome resolves when drug therapy is discontinued. Because human leukocyte antigen types of persons who develop myositis associated with D-penicillamine differ from those persons whose myositis is not associated with D-penicillamine exposure, individual factors such as immunologic or metabolizer genes or other cofactors may account for the finding that myositis develops in only a few persons exposed to these agents. Dermatomyositis has been reported as an immune-related adverse reaction to ipilimumab, a human monoclonal antibody targeted against cytotoxic T-lymphocyte antigen 4, which is used for the treatment of metastatic melanoma (Sheik et al 2015).

Pathophysiology of autophagous myopathy. Drugs with amphophilic cationic properties interfere with lysosomal digestion and lead to autophagous degeneration and accumulation of phospholipids in muscles and other tissues. An example of this type of myopathy is that caused by chloroquine, which produces peripheral neuropathy as well.

Pathophysiology of focal myopathy. Localized areas of muscle damage follow intramuscular injection as a result of needle insertion (needle myopathy). Myopathy may be due to traumatic necrosis, hematoma formation, or low-grade infection. Repeated intramuscular injections may lead to an area of fibrosis in the muscle. Focal myopathy may be due to local toxic effect of injected drugs. The primary side effect of intramuscular injection of botulinum toxin type A for cervical dystonia is an undesirable weakness of the muscle adjacent to the targeted muscle, but a spread to distant muscles may also occur.

Skin and soft tissue necrosis following intramuscular administration of various drugs, referred to as Nicolau syndrome, is considered to be likely due to damage to an end artery at the injection site (Uri and Behrbalk 2009).

Pathomechanism of drug-induced rhabdomyolysis. Drugs may have a direct toxic effect on the myocytes. The suggested mechanisms include the following:

- Inhibition of calcium metabolism by sarcoplasmic reticulum.
- Disruption of muscle cell membrane.
- Inhibition of Na-K adenosine triphosphatase and alterations in carbohydrate metabolism.
- Gene mutations for skeletal muscle diseases, which include enzymes from the glycolysis and glycogenolysis pathway and the pentose phosphate pathway, potentiate the risk for episodes of rhabdomyolysis (Hohenegger 2012).

Several drugs can cause muscle damage by inducing hypokalemia. These include thiazide diuretics, chlorthalidone, amphotericin B, laxatives, carbenoxolone, and licorice. Rhabdomyolysis occurring with hypokalemia is usually associated with potassium levels of 2 mmol/L or less. Hyponatremia has been associated with rhabdomyolysis in acute water intoxication. Drugs such as benzodiazepines, which produce hyponatremia, can also induce rhabdomyolysis. Depression of membrane potential induced by benzodiazepines could have had a synergistic effect in disrupting the cell membrane in these cases.

Rhabdomyolysis has now been associated with statin therapy. Cerivastatin withdrawal was prompted by an unacceptably high rate of rhabdomyolysis associated with its use. Other statins, pravastatin and fluvastatin, are least likely to provoke muscle cell damage because they are not metabolized by the cytochrome P-450 3A4 pathway. Muscle damage with HMG-CoA reductase inhibitors is usually the result of drug-to-drug interactions rather than a specific adverse response to HMG-CoA reductase inhibitor monotherapy. A case has been reported of rhabdomyolysis following coadministration of fluconazole and simvastatin, which promptly resolved after discontinuation of fluconazole, suggesting the possible role of drug interaction in the development of this adverse reaction (Hazin et al 2008).
Rhabdomyolysis is a feature of 2 other drug-induced disorders: neuroleptic malignant syndrome and malignant hyperthermia (which is usually triggered by anesthetic agents). Rhabdomyolysis following accidental injection of a local anesthetic agent into the femoral artery during coronary angiography has been reported (Selimoglu et al 2009). Factors contributing to drug-induced rhabdomyolysis are:

Drug overdose. In a case of drug overdose, the following factors contribute to rhabdomyolysis:

- Seizures
- Muscle compression, occlusion of regional blood supply, or both
- Metabolic acidosis
- Hypoxia
- Prolonged coma with immobilization

Psychiatric patients. These patients are at risk for development of rhabdomyolysis for the following reasons:

- Motor hyperactivity, catatonia, or physical agitation. Creatine kinase values can rise to 2 to 3 times normal values in acute psychotic states.
- Overdosage of psychotropic drugs
- Physical restraints used to immobilize agitated patients
- Seizures, hyponatremia, and dehydration are seen more commonly in psychiatric patients.

Pathomechanism of myopathy associated with cholesterol-lowering agents. The pathomechanism of these myopathic changes is poorly understood, but various mechanisms have been considered.

- Statins impair mitochondrial function and alter intracellular signaling proteins, which can lead to myocyte apoptosis, or they can induce an autoimmune necrotizing myositis (Jones et al 2014).
- Statin-induced autoimmune myopathy is characterized by progressive muscle weakness, evidence of muscle cell necrosis on biopsy, as well as the presence of autoantibodies against 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Statin-induced overexpression of HMG-CoA reductase in genetically susceptible patients may cause autoimmunity against HMG-CoA reductase (Mammen 2016). According to this concept, following the breach of tolerance barrier, autoimmune response is activated, and high HMG-CoA reductase levels in muscle cells, which are trying to regenerate, continue to drive autoimmunity in spite of discontinuation of statin. It requires control with immunosuppressive therapy to prevent further deterioration.
- One explanation is that cholesterol is a major constituent of the muscle membrane, which is affected with an increase in “membrane fluidity” in patients receiving a variety of cholesterol-lowering drugs. This may result in unstable sarcolemma, myotonic discharges, and increased levels of sarcoplasmic enzymes or myoglobinuria. Simvastatin-induced myopathy in rabbits shows myotonic discharges on EMG, myonecrosis, and raised serum creatine kinase levels, suggesting that the pathomechanism of myopathy are lesions of the muscle surface membrane.
- An experimental study in rats showed that simvastatin-induced structural and functional alterations are more profound in the fast-twitch than in the slow-twitch muscles as determined by measurements of muscle contraction as well as drug-induced molecular changes by spectroscopy (Simsek Ozek et al 2014).
- HMG-CoA-reductase inhibitors, used as cholesterol-lowering agents, have been shown to produce dose-related myocytotoxicity in rats, and this effect is potentiated by the concomitant use of cyclosporin.
- The role of gene polymorphisms in predisposition to statin-induced myopathy is an area of active investigation. Statins are transported into hepatocytes by the organic anion transporting polypeptide C, which is encoded by the gene SLCO1B1. A genome-wide study in patients treated with simvastatin found significant association between single-nucleotide polymorphisms located within the SLCO1B1 gene on chromosome 12 and established myopathy (SEARCH Collaborative Group 2008).
• The decrease of the content of CoQ10 has been demonstrated in skeletal muscle accompanied by a limitation in maximal oxidative phosphorylation capacity in patients treated with simvastatin; these observations may explain statin-induced myopathy (Larsen et al 2013).

• Depletion of metabolites of geranylgeranyl pyrophosphate, and not inhibition of cholesterol synthesis, is considered to be the primary cause of HMG-CoA reductase-induced myotoxicity.

• Experimental studies on sedentary animals treated with statins have shown impaired performance on muscular exercise due to muscle weakness and increase of oxidative stress with susceptibility to myopathy as compared to untreated animals. Conditioning with exercise prior to statin treatment protected against decrease in muscle function (Meador and Huey 2011).

• In addition to myopathy, rupture of Achilles and tibialis anterior tendons following statin use has been reported in patients. An animal experimental study has shown that statins induce imbalance of extracellular matrix components and possibly induce microdamage in tendons (de Oliveira et al 2013).

Pathophysiology of zidovudine myopathy. Numerous “ragged red fibers” (also called AZT fibers) indicative of abnormal mitochondria have been found in the biopsy specimens from zidovudine-treated patients and are considered to be unique to AZT-induced myopathy. These mitochondrial abnormalities consist of sarcolemmal or central accumulation of red granular material and longitudinal or circumferential “red rimmed cracks” as well as increased neutral fat that is attributed to impaired mitochondrial control of fatty acid use. It is possible to distinguish AZT-induced myopathy from the inflammatory myopathy of AIDS, but it is not certain if AZT can induce myopathy in humans in the absence of AIDS.

Mitochondrial DNA is reduced in muscle biopsy specimens in AZT-induced myopathy. This is reversible with discontinuation of the drug and is considered to be due to zidovudine-induced inhibition of mitochondrial DNA replication by DNA polymerase gamma T. The mechanism of AZT myotoxicity, however, is not explained by alterations in total mitochondrial DNA content. AZT myopathy is part of a wider disorder affecting cellular function in other tissues as well. AZT is now recognized to be a unique muscle mitochondrial toxin, causing depletion of muscle mtDNA, which results in myopathy.

Steroid myopathy. The basic cellular action of corticosteroids seems to be an inhibition of messenger RNA synthesis that, in turn, influences the translation and synthesis of muscle-specific proteins. Glucocorticoids impair glucose handling and promote protein catabolism. Myopathy is more likely to develop in patients treated with 9-alpha-fluorinated corticosteroids, such as triamcinolone, betamethasone, and dexamethasone. Denervation and disuse due to physical inactivity increase the susceptibility to corticosteroid myopathy. Fast-twitching glycolytic (type 2b) fibers are more susceptible in steroid-induced myopathy, but the cause is uncertain.

Epidemiology

Steroid myopathy. As manifested by clinically detectable proximal muscle weakness, steroid myopathy is seen in as many as 60% of patients receiving steroids (Batchelor et al 1997).

Cholesterol-lowering agents. Various studies estimate that 10% to 15% of statin users develop statin-related muscle side effects ranging from mild myalgia to more severe muscle symptoms with significant CPK elevations. The incidence of myopathy is approximately similar for all lipid-lowering drugs and is in the range of 0.1% to 0.5% with monotherapy, increasing to 0.5% to 2.5% with combination therapy (Hodel 2002). Fibrates are associated with a slightly increased risk (<1.0%) for myopathy (Davidson et al 2007). Although a transient increase in serum creatine kinase is common after treatment with lovastatin, clinically manifest myopathy has been reported in less than 1% of patients on this drug. The incidence of myopathy in patients treated with statins, estimated from cohort studies supported by randomized trials, was 11 per 100,000 person-years (Law and Rudnicka 2006). The incidence of statin-induced autoimmune myopathy is approximately 2 to 3 per 100,000 patients treated with statins.

Approximately 1 case of rhabdomyolysis is reported for every 100,000 treatment-years. Of 4000 patients participating in several clinical trials with this drug, 17 cases (0.04%) of lovastatin-associated rhabdomyolysis were reported. Cerivastatin was the most commonly implicated statin and has been removed from the market. There is an extremely
low risk for myopathy and rhabdomyolysis associated with lovastatin (Wortmann et al 2005).

Mitochondrial myopathy with zidovudine. Clinical and biochemical evidence of myopathy was seen in 17% of the AIDS patients who had been receiving zidovudine for more than 260 days and in none of those on short-term therapy.

Prevention

The following measures are suggested for preventing drug-induced myopathy:

• The monitoring of patients receiving drugs known to produce myopathy for early detection and discontinuation of medication.

• Avoidance of known risk factors such as alcohol consumption.

• Avoidance of depolarizing muscle relaxants such as suxamethonium during general anesthesia in patients susceptible to myotonia. Depolarizing muscle relaxants should be substituted with nondepolarizing relaxants. Some of the nondepolarizing neuromuscular blocking agents, such as doxacurium chloride, are steroid-based and can also lead to myopathy if combined with high-dose steroids.

• Overdosage of suspected drugs should be avoided.

• Avoidance of a combination of the simultaneous use of 2 drugs known to cause myopathy. Combination of colchicine with cyclosporin in renal transplant patients increases the risk of development of myopathy.

• Avoidance of a combination of neuromuscular blocking agents with corticosteroids, because this increases the risk of myopathy.

• Identification of patients with genetic susceptibility to adverse effects of certain drugs might help to avoid the use of drugs that are prone to induce myopathy in such patients. Further advances in pharmacogenetics should enable this.

• A randomized, double-blind trial has shown that the incidence of myopathy is approximately 3 times as high with the 80 mg dose of simvastatin compared to the equally effective 20 mg dose of atorvastatin (Egan and Colman 2011). Therefore, it is recommended that the 80 mg dose of simvastatin should be restricted to only those patients who have been taking it for a long time without symptoms of myotoxicity.

Differential diagnosis

Differential diagnosis of myopathy, whether due to drugs or other causes, follows the same clinical pattern. The attempt is not to prove the diagnosis of a particular drug-induced myopathy, but to determine if a drug is responsible in a patient undergoing investigations for myopathy. The most important consideration is the history of intake of a drug reported to cause myopathy. Recovery of the patient after discontinuation of the offending drug is further proof that myopathy is drug-induced. Some points of importance are as follows.

Differentiation of myopathies and neuropathies. This is important because HMG-CoA-reductase inhibitors can, in addition to causing myopathy, also produce neuropathy (de Langen and van Puijenbroek 2006). Motor and sensory nerve conduction studies and F-wave and H-reflex studies may be appropriate to exclude the possibility that the patient’s symptoms are due to a peripheral neuropathy or even to confirm the coexistence of a neuropathy. Chronic alcohol abuse is a common cause of toxic myopathy as well as peripheral neuropathy.

Differentiation diagnosis of muscle pain. Muscle pain can be a manifestation of some myopathies and of several other conditions. Drug-induced myalgia without any muscle weakness usually resolves promptly after withdrawal of the drug. Finding of muscle weakness and elevated serum creatine kinase levels suggests a necrotizing myopathy, and a muscle biopsy is required for the confirmation of diagnosis.

Hypokalemic myopathy. This is usually caused by diuretics. Hypokalemic myopathy differs from hypokalemic periodic paralysis as follows:

• There is an underlying cause such as a drug or disease. In hypokalemic periodic paralysis, the cause of hypokalemia is unexplained.
• Muscle glycogen is absent, whereas in hypokalemic periodic paralysis muscle is overloaded with glycogen.
• Enzymes derived from muscles are elevated and rhabdomyolysis may occur, whereas such an event is not a presenting feature in hypokalemic periodic paralysis.
• It requires a large quantity of therapeutic potassium supplementation for an extended term until recovery.

**Steroid myopathy.** Serum levels of creatine kinase and other enzymes are normal in steroid myopathy. If creatine kinase is elevated, another type of myopathy should be considered. EMG shows myopathic changes in proximal muscles with reduction in motor unit duration and amplitude without spontaneous muscle fiber potentials. Muscle biopsy shows a characteristic atrophy of type 2 muscle fibers.

**Differential diagnosis of inflammatory myopathies.** Patients with autoimmune disease are hypersensitive to cholesterol-lowering drugs. Muscular symptoms in patient on treatment with cholesterol-lowering drugs may be the first symptom of a polymyositis precipitated by this treatment and is an indication for antinuclear antibodies screening, particularly if there is proximal muscular weakness along with increased muscle enzyme levels (Fauchais et al 2004).

Macrophagic myofasciitis is an inflammatory myopathy. Genetic predisposition probably accounts for the variability in the prevalence of macrophagic myofasciitis in different populations. Intramuscular injection of aluminium-containing vaccines may produce myofasciitis that is characterized by a typical muscular infiltrate of large macrophages with aluminium inclusions (Di Muzio et al 2004).

Muscle biopsy is essential for confirmation of the diagnosis of inflammatory myopathy, although clinical diagnosis of muscle weakness and characteristic skin changes is suggestive of a patient with a connective tissue disorder. Immunohistological techniques are used for studying immune complex deposition, major histocompatibility complexes, and intracellular adhesion molecule expression. Investigations are directed towards any underlying immune or infective disorder or malignancy. Diagnosis of drug-induced myositis is based on history of drug use and exclusion of other causes.

**Critical illness myopathy.** Differentiation between drug-induced and nondrug-induced myopathy in critically ill patients is important in order to avoid unnecessary investigations and unreasonably pessimistic prognosis. Electromyography is essential for the diagnosis and for planning further clinical management. Biopsy needs to be done only when necessary.

**Differential diagnosis of rhabdomyolysis and myoglobinuria.** Various hereditary and acquired disorders may lead to episodes of severe, widespread muscle fiber destruction and myoglobinuria.

**Malignant hyperthermia.** In patients with malignant hyperthermia, muscle rigidity, fever, and rhabdomyolysis develop during anesthesia (halothane or other inhalational agents) in susceptible patients. Laboratory findings include a rise in serum creatine kinase and myoglobinuria. Rhabdomyolysis may also occur. However, such episodes may also be triggered by stress, strenuous physical activity, or a systemic infection. Patients presenting with rhabdomyolysis for the first time should undergo a detailed clinical assessment for drug-induced, toxic, or infective causes. Muscle biopsy and appropriate biochemical investigations should be done for detecting an underlying genetic disorder such as susceptibility to malignant hyperthermia or metabolic disorder. Malignant hyperthermia myopathy should be considered in the differential diagnosis. It is usually subclinical, but some muscle wasting may occur. Serum creatine kinase may be raised but is usually normal. Structural changes in the muscle are nonspecific.

**Neuroleptic malignant syndrome.** This syndrome should be considered in the differential diagnosis of patients with malignant hyperthermia and rhabdomyolysis. Some of the symptoms of neuroleptic malignant syndrome are similar to those of malignant hyperthermia: fever, muscle rigidity, myoglobinuria, and a rise in creatine kinase. One important difference is that neuroleptic malignant syndrome is usually associated with neuroleptic use in psychiatric patients and requires certain criteria for diagnosis. These include disturbances of consciousness and autonomic disturbances.

**Acute myopathy of intensive care.** This has been reported in critically ill patients treated with intravenous corticosteroids and neuromuscular junction-blocking agents in the intensive care unit. However, comatose and critically ill patients have been reported to develop muscle weakness or paralysis (quadriplegia) during the course of sepsis and multiple-organ failure where drugs such as steroids, neuromuscular-blocking agents, and aminoglycosides...
are not responsible for paralysis, and they may become completely paralyzed because of nondrug-induced neuromuscular disorders. The diagnosis is important to avoid unnecessary investigations and unreasonably pessimistic prognosis. Electroneurography and electromyography of peripheral nerves and muscles are essential for the diagnosis and for planning further clinical management. Biopsy should be done only when necessary.

Diagnostic workup

The first step in diagnosis involves a thorough neurologic examination with particular emphasis on the evaluation of muscle strength, muscle atrophy, sensory examination, and tendon reflexes. The important laboratory investigations are as follows:

- Serum creatine kinase. This is the most sensitive indicator of muscle damage. Elevated creatine kinase levels in serum indicate their leakage out of damaged muscles into the blood stream. Creatine kinase levels, which are more than 10 times the upper limit of normal, indicate drug-induced myopathy. Isoenzymes of creatine kinase are used to distinguish skeletal muscle damage from myocardial damage or damage to brain or nerve tissue. Slight increases in serum creatine kinase (up to 3 times the normal maximum concentration) are not necessarily due to muscle disease and may occur transiently as a result of strenuous exercise, minor muscle trauma including intramuscular injection, insertion of EMG needle electrodes, or viral illness.
- In patients who develop myopathy after statin exposure, a positive test for anti-HMG-CoA reductase autoantibodies strongly supports the diagnosis of an autoimmune process. One-third of the positive tests also occur in patients who have not been exposed to statins.
- EMG may show evidence of muscle damage, but similar changes may be seen in conditions that impair function of the neuromuscular junction. Nerve conduction studies may be helpful in differentiating the site of lesion.
- Muscle biopsy is required to provide a definitive diagnosis in the case of many muscle diseases. It is used to determine the site and extent of muscle damage and inflammatory changes, such as those that occur in myositis. Atrophy of type 2 fibers usually occurs early. Histochemical analysis of the biopsy specimen and electron microscopy enables differentiation of actin and myosin proteins of the myofilaments. The most common finding in diseased muscle is the disruption or destruction of the entire filament structure. These examinations are required for the definitive diagnosis of congenital myopathies. Diagnosis of autophagic vacuolar myopathy due to chloroquine, hydroxychloroquine, or colchicine currently requires electron microscopy which is costly and time-consuming. Immunohistochemical staining for either LC3 or p62 positive fibers, the percentage of which is significantly higher in the autophagic myopathy group compared to the normal control, improves the speed and accuracy of diagnosis (Lee et al 2012). Muscle cell necrosis and regeneration are the most prominent histologic features in muscle biopsy specimens from patients with statin-associated autoimmune myopathy.
- Muscle imaging by CT and MRI can provide information on the cross-sectional area of the limb or axial muscles and is, therefore, useful in detecting muscle atrophy. Radioisotope techniques with muscle scanning after administration can be useful for detection of areas of muscles involved in inflammatory myopathy.
- Molecular diagnosis is useful for the evaluation of a patient with muscle disease to identify the gene mutations causing the disease or increasing susceptibility for developing drug-induced myopathy in the patient or in a family.

Management

The basic treatment is discontinuation of the offending drug and symptomatic management of the complications. The approach to management depends on the drug and the type of myopathy induced. There are some preventive strategies as well.

Myopathy due to cholesterol-lowering agents. Diagnosis of statin myopathies should be based on pathophysiologic mechanisms, pathology as determined by biopsy, clearance properties of creatine kinase, drug
challenge/de-challenge/re-challenge, and differential diagnoses, rather than on temporal association with the drug to reduce diagnostic errors and healthcare costs (Kuncl 2009).

Myopathy may be avoided by identifying patients at risk of myotoxic effects such as the elderly or female patients, or those with concomitant medications or impaired metabolic processes. In a case-control study including first and second degree relatives, statin-induced muscle toxicity was significantly associated with susceptibility to malignant hyperthermia (Hedenmalm et al 2015). Genetic analysis for mutations relevant to statin myopathy may provide predisposition testing for safe use of statins (Vladutiu 2008).

Management options for patients who do not tolerate statins include switching to low-dose, non-daily doses of long-acting statins, such as rosuvastatin and atorvastatin, and other non-statin lipid-lowering agents, such as ezetimibe and colesevelam (Abd and Jacobson 2011). Myopathic symptoms usually resolve after discontinuing the offending statin, and the same statin can be restarted at a lower dosage, or patients can be switched to a different statin (Gillett and Norrell 2011). Because myotoxic events are more frequent at higher doses, statins that are effective at lower doses should be used. Supplementation with CoQ10 should be considered based on demonstration of its decreased level in muscles with statin use.

A rare case of compartment syndrome as a result of simvastatin-induced myositis has been reported and required 4-compartment fasciotomy (Walker et al 2008). Controlled trials of coenzyme Q supplementation in statin myopathy have yielded contradictory results.

Some patients with statin-induced autonomic myopathy improve spontaneously after discontinuation of the drug. If there is no improvement, immunosuppressive therapy should be initiated, similar to that for other forms of autoimmune muscle disease, eg, using oral prednisone or intravenous immune globulin.

**Corticosteroid myopathy.** Corticosteroid myopathy is the most frequent drug-induced myopathy and is characterized by muscle weakness without pain. It is usually reversible if the drug is withdrawn, if the dose is reduced, or if prednisone is substituted for a fluorinated glucocorticoids, such as dexamethasone. Corticosteroid-induced muscle atrophy and weakness can be partially prevented or reversed by a program of physical exercise. Experimental treatments include insulin-like growth factor-I, branched-chain amino acids, creatine, testosterone, nandrolone and dehydroepiandrosterone, and glutamine (Pereira and Freire de Carvalho 2011).

**Myopathy due to neuromuscular blocking drugs.** Management of these patients is mostly supportive, consisting of nutritional support, physical therapy, and gradual weaning from ventilatory support. According to published guidelines, neuromuscular blocking drugs should be used in critically ill patients only when absolutely necessary and when the depth of muscle paralysis can be monitored to avoid overdosing and accumulation of metabolites (Murray et al 2006).

**Mitochondrial myopathy due to zidovudine.** L-carnitine used concurrently with AZT in patients with AIDS has been reported to rescue the myotubules and their mitochondria from the AZT-associated destruction and lipid storage. One possible rationale of this effect is the observation that muscle biopsy in patients with AIDS who have zidovudine-induced myopathy have a reduction in muscle carnitine levels.

**Management of drug-induced rhabdomyolysis.** Guidelines recommended for the management of rhabdomyolysis are shown in Table 10.

**Table 10. Guidelines Recommended for Management of Rhabdomyolysis**

- Early detection
  - routine estimation of serum creatine kinase and urinary myoglobin
  - detection of localized areas of myonecrosis by CT scan
- Fluid replacement
- Bicarbonate infusion
  - to alkalinize urine and to prevent dissociation of myoglobin to its nephrotoxic metabolite ferrihemate
- Promotion of diuresis: mannitol
- to dilute nephrotoxic substances
- to flush through blocked renal tubules

• Treatment of complications of rhabdomyolysis
  - hyperphosphatemia: oral phosphate-binding antacids
  - hyperkalemia: usually corrects itself
  - renal failure: dialysis
  - disseminated intravascular coagulation: heparin useless
  - compartment syndromes: decompressive fasciotomy
  - seizures: anticonvulsants
  - hyperthermia: cooling

Special considerations

Anesthesia

Various anesthetic agents and depolarizing muscle relaxants are implicated in the causation of rhabdomyolysis. Malignant hyperthermia with rhabdomyolysis occurs in 1 out of 20,000 anesthetized adults who are presumed to have a genetic predisposition to it. Anesthetics may act as a trigger for the onset of rhabdomyolysis in patients with preexisting occult causes. Acute rhabdomyolysis has been reported after halothane. Anesthesia-induced rhabdomyolysis has been reported in infants with unsuspected Duchenne dystrophy. A dystrophin test in addition to creatine kinase determination should be considered for the detection of this condition in patients undergoing anesthesia.

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**References especially recommended by the author or editor for general reading.

**ICD and OMIM codes

**ICD codes

ICD-9:
Toxic myopathy: 359.4

ICD-10:
Myopathy due to other toxic agents: G72.2

**Profile

**Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance

male=female

**Family history
family history may be obtained

**Heredity**

none

**Population groups selectively affected**

none selectively affected

**Occupation groups selectively affected**

none selectively affected

**Differential diagnosis list**

muscle pain
polymyositis
macrophagic myofasciitis
drug-induced myalgia
hypokalemic periodic paralysis
connective tissue disorder
malignant hyperthermia
neuroleptic malignant syndrome
acute myopathy of intensive care

**Associated disorders**

Alcohol myopathy
Focal myopathy
Hypokalemic myopathy
Mitochondrial myopathy
Myalgia
Myositis
Neuroleptic malignant syndrome
Rhabdomyolysis
Steroid myopathy

**Other topics to consider**

Corticosteroid myopathies
Drug-induced neurologic disorders
Polymyositis and fasciitis
Viral and retroviral myositis

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