Drug-induced myopathies

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Purpose of review

Drug-induced muscle disorders are important causes of morbidity, but the risk–benefit profile of the incriminated drugs must be put into perspective. This review highlights some recent advances on statin-induced and antiretroviral drug-induced myopathies and calls attention to some less familiar myotoxic disorders.

Recent findings

In statin myopathy, reduction of coenzyme Q has been discussed as a key mechanism. However, data on coenzyme Q concentration and mitochondrial dysfunction in muscle of these patients are not conclusive. The first two controlled trials on coenzyme Q supplementation in statin myopathy have yielded contradictory results and do not support a routine supplementation. In human immunodeficiency virus infection, the advent of highly active antiretroviral therapy has led to a shift from virus-related to drug-induced morbidity. The knowledge of these distinct syndromes allows rational management. In addition, an omnium-gatherum is presented with recent findings on drug-induced dermatomyositis, tendinopathy, rhabdomyolysis, and local myotoxicity. These latter topics are intended to direct attention to less familiar but still clinically relevant myotoxic events.

Summary

Statin myotoxicity may be prevented in many cases by anticipation of drug–drug interactions. On the contrary, undue withdrawal of statins owing to minor myalgias should be avoided. A large and appropriately powered trial is required to finally determine whether supplementation of coenzyme Q can mitigate statin myopathy. The identification of individual genetic risk factors for myotoxicity is a key challenge for future pharmacogenomic research.

Keywords

antiretroviral therapy, coenzyme Q, myotoxicity, pharmacogenomics, statin

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Introduction

Adverse drug reactions (ADRs) are a major cause of morbidity and mortality. In different series worldwide, they account for approximately 5% of all hospital admissions and 5% of all fatalities [1]. Muscle is particularly prone to ADRs for several reasons. First, it is highly exposed to circulating drugs due to its mere mass (around 45% of total body weight) and high blood flow. Second, its mitochondrial energy metabolism seems to be a preferred target for many drugs. This review covers recent observations on myopathies caused by statins and antiretroviral drugs as well as some less familiar topics.

Statin myopathy

Statins lower cholesterol by inhibiting 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase, the key enzyme of cholesterol synthesis. The efficacy of these drugs in the prevention of cardiovascular events is beyond dispute, and each of the currently available statins is also considered to have a very good safety profile. Myotoxicity, however, is a concern, but there is ongoing controversy about its frequency, mechanisms, genetic determinants and clinical management.

Epidemiology

Data on the incidence of muscle complaints with statin use vary markedly between studies. This is mainly due to discordant definitions of myopathy and to the differences between controlled trials and postmarketing surveillance. Applying the definitions of the US National Lipid Association Statin Safety Assessment Task Force [2], a meta-analysis of 21 clinical trials providing 180 000 person-years of follow-up found that myopathy, defined as muscle symptoms and creatine kinase levels above 10-fold upper limit of normal (ULN), occurs in five patients per 100 000 person-years, and rhabdomyolysis, defined as creatine kinase more than 10 000 IU/l or creatine kinase more than $10 \times \text{ULN} +$ elevation in serum creatinine or requirement for hydration therapy,

in 1.6 patients per 100 000 person-years [3]. Less severe manifestations are much more common. Myalgias with or without creatine kinase elevation affect 2–7% of patients, and asymptomatic creatine kinase elevation up to 10-fold ULN is noted in 11–63% of patients [4]. After the withdrawal of cerivastatin, the risk of myotoxicity appears roughly the same among all marketed statins. This is also true for the most recently approved rosuvastatin [5,6•].

Mechanisms

The ultimate cause of statin myopathy is unknown, but possible mechanisms include decreased sarcolemmal cholesterol, mitochondrial dysfunction from reduction of coenzyme Q (CoQ), and depletion of key isoprenoids that control myofiber apoptosis. The observation that characteristic structural abnormalities of statin myopathy can be reproduced by extraction of cholesterol from skeletal muscle fibers *in vitro* supports the hypothesis that cholesterol lowering *per se* contributes to myocyte damage and suggests further that it is the specific lipid/protein organization of the skeletal muscle cell itself that renders it particularly vulnerable [7].

The competing mitochondrial theory is based on the fact that statins inhibit the synthesis of mevalonate, a precursor of both cholesterol and CoQ. Statins have been known to reduce circulating CoQ levels in humans since 1990 [8], and this finding was reproduced in nearly 20 studies [9•]. However, the significance of these data has recently been questioned. As plasma CoQ is transported with lipoproteins, the CoQ decrease seems largely due to statin-induced reduction in lower density lipoproteins. With regard to tissue concentrations, animal studies found CoQ reductions in heart and liver, but data on skeletal muscle are inconsistent [10]. In humans, low-dose statin treatment does not appear to reduce intramuscular CoQ concentrations [9•] except for a subgroup of 16 patients receiving simvastatin 80 mg/day in one study [11]. If reduced CoQ levels are to mediate statin myopathy, there should also be evidence of impaired mitochondrial function. Again, results from animal and human studies are inconsistent in this regard. In a recent study employing muscle biopsies from 18 patients, only two had mild signs of mitochondrial dysfunction [12].

The key question is whether CoQ supplementation can mitigate statin-induced myopathic symptoms. The first controlled trials on this were published in 2007, but again the data are contradictory. Caso *et al.* [13••] randomized 32 statin-treated patients with myalgias to receive 100 mg/day CoQ or 400 IU/day vitamin E for 30 days. In the CoQ group, pain severity and pain interference with daily activities decreased by approximately 40%, whereas no changes occurred in the vitamin E group. The authors concluded that CoQ supplementation may offer an alternative to the discontinuation of statins. Young *et al.* [14••], however, found no improvement in myalgias or statin tolerance in 44 patients randomized to 200 mg/day CoQ or placebo for 12 weeks.

Taken together, key issues on the relations between statins and CoQ remain unresolved. A large and appropriately powered trial is required to finally determine whether the safe and simple supplementation with CoQ can reduce statin myotoxicity. In the meantime, individual attempts may be warranted in selected patients.

Genetic determinants

Statin tolerability is modified by several genetic and nongenetic factors. For example, atorvastatin-induced muscle toxicity has been shown to be more severe in younger people (conceivably due to higher muscle mass) and in men (conceivably due to slower metabolism) [15]. Some genetic variations associated with statin myotoxicity have been described [16••] and include polymorphisms in cytochrome P450 (CYP) enzymes that accomplish the oxidation of most statins (phase I metabolism), polymorphisms in uridine diphosphate (UDP)-glucuronosyltransferase-1 (UGT1) that further modifies the statin derivatives (phase II metabolism), and polymorphisms in membrane transporters altering the cellular uptake of statins, for example, in the solute carrier organic anion transporter (SLCO) family. Moreover, occult metabolic muscle defects have been shown as a predisposing factor in some case reports or small studies. Among 136 patients with statin-induced myopathies, Vladutiu *et al.* [17] found that approximately 10% of patients were heterozygous or homozygous for disease-causing mutations in rare metabolic myopathies, namely myoadenylate deaminase deficiency, McArdle disease, and carnitine palmitoyl transferase II deficiency. In another study, two polymorphisms in the *COQ2* gene (encoding the second enzyme of CoQ biosynthesis) were significantly associated with statin intolerance in 133 patients as compared to 158 controls [18•]. Finally, a temporal relation of symptoms to statin therapy was observed in a mitochondrial encephalomyopathy, lactic acidosis and stroke-like episode (MELAS) patient [19].

Since the sequencing of the human genome, there has been much talk about personalized medicine. The identification of genetic risk factors for ADRs in individual patients is a key challenge for future pharmacogenomic research [16••,20•].

Clinical management

In my opinion, there are two common and preventable mistakes with regard to statin myotoxicity. First, there is too little attention to possible drug–drug interactions at the commencement of statin therapy or of concomitant therapy. Most cases of severe statin myopathy or

Table 1 Drugs that increase statin toxicity

Inhibitors or competitors at CYP 3A4 leading to increased statin concentration and toxicity	
Antibiotics	Erythromycin
Antifungal agents	Ketoconazole
HIV protease inhibitors	Ritonavir
Immunosuppressive drugs	Cyclosporine, tacrolimus
Cardiac drugs	Verapamil, amiodarone
Anticoagulants	Warfarin
Psychopharmacologics	Fluoxetine, diazepam
Others	Cimetidine, grapefruit juice

rhabdomyolysis do not occur with monotherapy but relate to pharmacokinetic interactions with other agents. The most important interaction pertains to the hepatic CYP system that controls the metabolism of most statins [21•]. For example, drugs that inhibit or compete with the CYP 3A4 isoenzyme (Table 1) lead to increased plasma levels and consequently increased toxicity of lovastatin, simvastatin, and atorvastatin. If the coadministration of drugs cannot be avoided, the risk of adverse effects may be lowered by dose adjustment or by switching to pravastatin, fluvastatin, or atorvastatin that are not significantly metabolized by CYP 3A4. Other modes of interaction have to be kept in mind, however. For example, cyclosporine inhibits not only CYP 3A4, but also the P-glycoprotein transmembrane pump and the hepatic statin transporter. As a consequence, cyclosporine interferes with the pharmacokinetics of all statins, and the necessity of this combination should be thoroughly reconsidered. Another combination that leads to a high incidence of severe muscle damage and should therefore be avoided is that of statins and other lipid-lowering agents, particularly fibrates.

The second momentous mistake in the management of statin-induced muscle complaints is the undue withdrawal of statins just because of asymptomatic creatine kinase elevation or mild and tolerable myalgias. Minor muscle symptoms are very common with statins, and in most cases do not herald a major event. As statins reduce cardiovascular endpoints by approximately 30%, they should not be withdrawn without a good reason. A management algorithm for statin-induced myotoxicity is provided in Fig. 1.

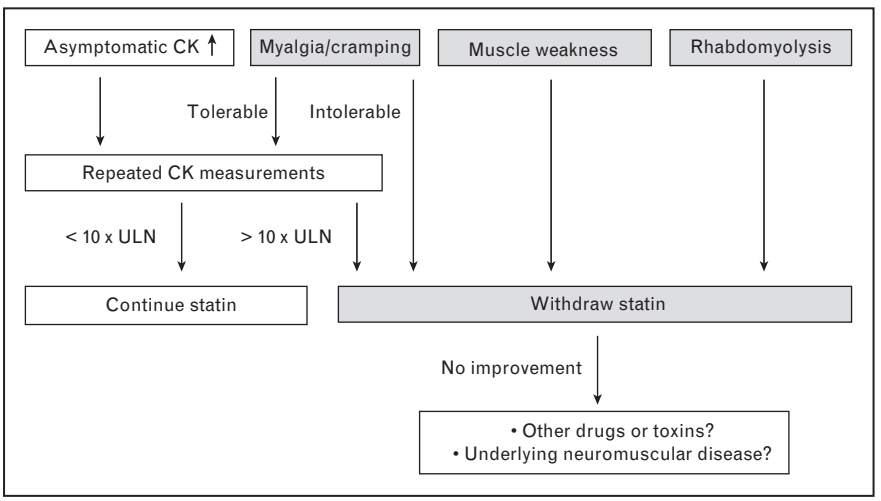
HIV, highly active antiretroviral therapy, immune restoration inflammatory syndrome, and the muscle

Skeletal muscle involvement may occur at all stages of human immunodeficiency virus (HIV) infection, and can be classified as follows: HIV-associated myopathies and related conditions, including polymyositis, inclusion-body myositis, nemaline myopathy, diffuse infiltrative lymphocytosis syndrome, HIV-wasting syndrome, vasculitis, and myasthenic syndromes; opportunistic infections and tumor infiltrations of skeletal muscle due to insufficient immune defense; and muscle complications of antiretroviral therapy. Introduction of nucleoside-analogue reverse transcriptase inhibitors (NRTIs) in 1987, protease inhibitors in 1996, and, in particular, their combination as highly active antiretroviral therapy (HAART) has led to a dramatic decline in virus-related morbidity and mortality. In turn, the prevalence of antiretroviral drug-induced syndromes increased markedly.

Nucleoside-analogue reverse transcriptase inhibitors

NRTIs such as zidovudine (AZT), stavudine (d4T), didanosine (ddI), zalcidabine (ddC), and lamivudine (3TC) exert their effect through competition with the natural substrates of HIV reverse transcriptase. By the same

Figure 1 A management algorithm for statin-induced myotoxicity



CK, creatine kinase; ULN, upper limit of normal.

mechanism, however, they interfere with the mitochondrial DNA (mtDNA) polymerase gamma (POLG), the key enzyme of mtDNA replication. Accordingly, NRTIs can lead to a mitochondrial myopathy with ragged red and cytochrome c oxidase (COX)-deficient muscle fibers, biochemical COX defect, high blood lactate, and mtDNA depletion [22]. This so-called zidovudine myopathy occurs after high cumulative doses of the drug, and manifests with insidious onset of myalgia, muscle tenderness, proximal weakness, and creatine kinase elevation. It is clinically indistinguishable from HIV polymyositis. This condition is reversible after discontinuation of drugs.

Another syndrome presumably due to NRTI-induced mtDNA depletion manifests with severe hepatic steatosis, pancreatitis, lactic acidosis, and mitochondrial myopathy with lipid accumulation [23]. Early detection of this life-threatening condition may be ensured by monitoring of lactate, creatine kinase, and liver enzymes. MtDNA depletion precedes the other markers and may also be monitored in blood lymphocytes [24].

Protease inhibitors

Adverse effects of protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir) are based on the unintentional inhibition of the body's own proteases, leading finally to insulin resistance and central fat accumulation. The characteristic HIV-associated lipodystrophy with central fat accumulation and peripheral fat atrophy phenotypically resembling multiple symmetric lipomatosis results from the combined adverse effects of protease inhibitors and NRTIs.

In addition, protease inhibitors lead to increased fatty acid and cholesterol biosynthesis. Treatment with statins and fibrates must be thoroughly weighed, however, as protease inhibitors also increase the concentration of statins due to pharmacokinetic interactions at the CYP system with an increased risk of rhabdomyolysis [25•]. Rosuvastatin appeared to be an effective statin in hyperlipidemic HIV-infected patients, as it undergoes only minimal metabolism by CYP. While protease inhibitor levels were not affected by this statin, rosuvastatin levels increased 1.6-fold, however. Until safety and efficacy have been confirmed in larger studies, the combination of rosuvastatin and protease inhibitors should also be used with caution [26]. Other HIV-associated drugs implicated in rhabdomyolysis include didanosine, lamivudine, and trimethoprim–sulfamethoxazole.

Immune restoration inflammatory syndrome

HIV patients treated by HAART may develop paradoxical inflammatory responses due to reconstitution of the previously incompetent immune system, a phenomenon termed immune restoration inflammatory syndrome (IRIS). This includes overt inflammatory responses directed against afore quiescent pathogens such as tuberculosis [27•] as well as flare-up of autoimmune inflammation, such as sarcoidosis and polymyositis [28]. Ironically, clinical presentation and muscle biopsy findings are largely indistinguishable in HIV polymyositis and IRIS polymyositis, but one indicates immune compromise and the other immune restoration. Management of autoimmune processes in HIV patients often requires immunosuppressive agents, but this is obviously problematic as it may further weaken the immune system.

Drug-induced dermatomyositis

Dermatomyositis is clinically characterized by proximal muscle weakness, creatine kinase elevation, photodistributed erythema, heliotrope rash, and Gottron's papules. The key pathological finding is autoimmune injury to the microvascular endothelium, mediated by antibodies and complement activation. Endothelium may become antigenic by infection with endotheliotropic viruses such as parvovirus B19 and cytomegalovirus or by molecular mimicry in the setting of paraneoplastic dermatomyositis. Drug-induced dermatomyositis has only rarely been described. The incriminated compounds include statins, fibrates, hydroxyurea, penicillamine, omeprazole, niflumic acid, phenytoin, tegafur, interferon α, silicon gel, bacille Calmette-Guérin (BCG) tuberculosis vaccine, alfuzosin and, recently, the antifungal agent terbinafine [29•]. Importantly, many of these drugs (including statins) have also been implicated in other autoimmune diseases, most notably systemic and cutaneous lupus erythematosus [30•]. The mechanisms by which drugs may induce autoimmunity involve promotion of apoptosis leading to exposure of new antigens and enhancement of innate immune response. Exemplarily, both pathways have been demonstrated for terbinafine [29•]. In contrast to other toxic effects, drug-induced autoimmune responses may persist despite cessation of the responsible compound, and immunosuppressive therapy is often required.

Fluoroquinolones: it is not always the tendon

Fluoroquinolones (ofloxacin, norfloxacin, levofloxacin, ciprofloxacin) are frequently used antibiotics that are considered as relatively safe and well tolerated. Tendinopathy and tendon ruptures, however, are well recognized side effects of these drugs and may be mediated by induction of matrix metalloproteinases and subsequent compromise of tendon microstructure [31]. Patients typically complain of pain after some days of treatment. Clinical findings include tendon swelling, warmth, and tenderness. The Achilles tendon is most commonly involved. Up to 50% of patients may develop tendon rupture, particularly those who are simultaneously taking corticosteroids [32]. A case–control study showed that one case of Achilles tendon rupture occurs for every 5958 persons treated.

The corresponding number needed to harm is 1638 for those aged more than 60 years and 979 for patients who concomitantly use corticosteroids [33]. As tendinitis mostly recovers and tendon rupture may be prevented with the discontinuation of the drugs, clinicians should be aware of this adverse effect.

Apart from tendinopathy, the fluoroquinolone antibiotics have been implicated in rhabdomyolysis. Rare cases have been described with ofloxacin [34], norfloxacin [35], and levofloxacin [36]. As in all cases of drug-induced rhabdomyolysis, discontinuation of the drug is mandatory.

Local myotoxicity

Many drugs cause direct muscle damage after application into or in nearby muscles. As this does not lead to functional impairment in most cases, this topic is only rarely discussed in neurologic journals. There are, however, some instances of clinically important sequelae of local injections.

Local anesthetics and eye muscles

Myotoxicity of local anesthetics has long been recognized. Animal models have shown a rather uniform course of injury: muscle edema and hypercontracted myofibrils are evident minutes after injection, followed by lytic degeneration of sarcoplasmic reticulum and mitochondria; after 1–2 days, cellular debris is cleared by macrophages; as myoblasts, basal lamina, vessels, and nerves remain intact, mostly complete regeneration ensues within 3–4 weeks [37]. Experimentally, all local anesthetics are myotoxic with procaine producing the least and bupivacaine the most severe injury. Although this damage typically carries no weight in large skeletal muscles, there are several reports on transitory or persistent diplopia after otherwise uneventful cataract surgery. In a large series, the incidence of anesthesia-related persistent vertical diplopia was 0.39% with retrobulbar application of the local anesthetic. This was considered most likely because of direct damage to the inferior rectus muscle by the needle or the anesthetic [38] that can also be visualized by magnetic resonance imaging [39]. After some weeks, regeneration of the damaged muscle may lead to restitution or through consecutive hypertrophy to persistence of diplopia [40]. The same bupivacaine-induced cycle of myotoxicity, degeneration, regeneration, and hypertrophy of muscle fibers is investigated in animal models as a treatment option. Recently, a single patient with paretic strabismus was reported with resolution of diplopia after bupivacaine injection of the right lateral rectus muscle [41•].

Contractures

Frequently repeated intramuscular injections in the same site can lead to local induration, fibrosis, and finally contractures requiring surgery. This type of reaction depends on site of injection, age of patient, and physicochemical properties of the pharmacological agent and its galenic preparation. It has most commonly been associated with narcotics abuse and with frequent intramuscular application of antibiotics in children. Most commonly involved are the quadriceps [42], triceps [43], and deltoid [44•] muscles.

Nicolau syndrome

Another complication after intramuscular drug injection is Nicolau syndrome. As denoted in the synonym embolia cutis medicamentosa, this is a local tissue necrosis due to ischemia. The latter may be caused by embolism after incidental intraarterial injection of the drug or by vasospasm after periarterial injection. This adverse event is clinically characterized by severe pain and whitening or livedo-like changes of the skin immediately after an intramuscular injection. Necrosis may not only involve the skin but also the subjacent muscle leading to rhabdomyolysis. The syndrome was first described in the 1920s in patients treated for syphilis with bismuth salts, but since then many compounds have been implied including penicillins, local anesthetics, antihistamines, corticosteroids, and diclofenac [45•].

Conclusion

Apart from the compounds covered in this review, hundreds of other drugs can cause muscle damage. As drug-induced myopathy frequently resolves after discontinuation of the offending agent, physicians should be alert to this. Moreover, it is evident that most myotoxic events are not due to single drugs but to drug–drug interactions. The most prominent and clinically relevant examples are any combinations of statins, fibrates, cyclosporine, and protease inhibitors. Many myotoxic events could be avoided by prudent choice of drugs or dose adjustment. On the contrary, undue withdrawal of statins just because of asymptomatic creatine kinase elevation or mild and tolerable myalgias is not necessary and even dangerous given the undisputed benefit of statins for cardiovascular endpoints. With regard to CoQ supplementation in order to mitigate statin myopathy, two recent trials were underpowered and a large controlled trial is required. The identification of individual genetic risk factors for myotoxicity is a key challenge for future pharmacogenomic research.

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