Toxic Myopathies

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KEYWORDS

• Toxic myopathies • Muscle tissue • Statins • Myopathy

KEY POINTS

- Many drugs have potential to cause muscle damage, including commonly prescribed medications, such as statins.
- A good medical history, including current and previous medication history, should be obtained; stopping the offending agent usually leads to improvement of myopathy because muscle cells have the capacity to regenerate.
- Continued use, however, and immune-mediated myopathies can be associated with significant morbidity and mortality.

INTRODUCTION

Many substances, including commonly prescribed medications, can produce adverse effects on muscle.[1–4] Alcohol, one of the oldest substances known, has an ability to cause muscle weakness that has been recognized since the middle of nineteenth century.[5] Adverse effects of pharmaceuticals on muscles have been described mostly within the past 50 years. Cholesterol-lowering medications, in particular the statins,[3,6–9] have been the most commonly prescribed drugs that have been described to cause a myopathy in recent years, and autoimmune mechanisms are discussed in the idiopathic inflammatory myopathy article in this issue by Dimachkie. Medications can have a direct or indirect adverse effect on the muscle. Direct effect can be focal, as might occur secondary to drug injected into tissue, or generalized. Indirect toxic effects may result from the agent creating an electrolyte imbalance or inducing an immunologic reaction. Clinical manifestations of toxic myopathies range from muscle pain to more serious muscle damage, leading to rhabdomyolysis.[1,10] Although some categories of drugs are associated with specific forms of myopathies,

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a drug can cause more than one type of 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 the management of these patients.

Clinical presentation

Clinical manifestations of drug-induced myopathy are often indistinguishable from those of myopathies due to other causes, as well as from idiopathic forms. Clinical manifestations can be varied and with combination of various symptoms including diffuse myalgia (muscle pain and stiffness) without any other neurologic signs, painless proximal myopathy (weakness), painful myopathies, focal myopathy with focal area of damage due to injections, myokymia or rhythmic rippling of muscles, mitochondrial myopathy associated with inhibition of mitochondrial DNA and characterized by ragged red fibers, rhabdomyolysis with myoglobinuria, malignant hyperthermia, and secondary effects of myopathies.

PATHOPHYSIOLOGY/PATHOGENESIS

Based on pathogenic mechanisms, 7 main categories of toxic myopathies are recognized[3,4]: (1) necrotizing myopathy, (2) amphiphillic myopathies, (3) antimicrotubular myopathy, (4) mitochondrial myopathy, (5) inflammatory myopathy, (6) hypokalemic myopathy, and (7) steroid myopathy/critical illness myopathy (**Table 1**).

NECROTIZING MYOPATHY

Introduction

Several drugs can cause a generalized necrotizing myopathy, with cholesterol-lowering drugs the major cause of this type of myopathy.[11,12] Other agents include the immunophilins (cyclosporine and tacrolimus); rarely, the antihypertensive agent labetalol; and propofol. With statins, besides toxic necrotizing myopathy, which stops with discontinuation of the medication, recent evidence suggests that they also trigger an autoimmune myopathy that progresses for months after statin discontinuation, referred to as statin-associated necrotizing autoimmune myopathy (SANAM) (see idiopathic inflammatory myopathy article in this issue by Dimachkie).

Statins

Clinical presentation

Although myalgias, weakness, or asymptomatic elevation of creatine kinase (CK) levels[6] occur with statin exposure, severe necrotizing myopathy may be complicated by myoglobinuria and renal failure. The degree of serum CK elevation is proportionate to the amount of muscle damage. Proximal weakness develops after periods of statin exposure, ranging from weeks to years in SANAM. The weakness usually progresses beyond 2 months after statin cessation in the autoimmune variant whereas patients with toxic necrotizing myopathy stabilize in strength and markedly improve within 2 to 3 months of statin cessation. The CK levels are markedly elevated. A retrospective chart review performed at the University of Kansas Medical Center showed 11 of 18 (61%) patients on statins having SANAM and 7 of 18 (39%) with toxic necrotizing myopathy (**Table 2**). Mean age of onset was 55, with more women than men, and disease duration on presentation was 2 to 12 months (see **Table 2**). Proximal leg weakness was the most common presentation with SANAM; few had proximal arm weakness and neck flexor weakness. Respiratory or bulbar dysfunction was not seen in the authors' patients.[13]