10. Antibiotics – associated myopathies: The current update

Miroslav Radenković

Department of Pharmacology, Clinical Pharmacology and Toxicology, Medical Faculty, University of Belgrade, P.O. Box 38, 11129 Belgrade, Serbia

Abstract. The muscle tissue appears particularly susceptible to drug–related injuries. Drug–related myopathies can vary in their clinical presentations, starting from mild myalgias, going through myositis, all the way to severe rhabdomyolysis. At the cellular level, drug–associated myopathies most generally result in necrosis, vacuolar changes, or mitochondrial dysfunction. The most common factors that increase the risk of drug–induced myotoxicity include: advanced age, administration of multiple myotoxic drugs, high doses of myotoxic drugs, female gender, thyroid disease, existing hepatic or renal disease, perioperative period of surgery, existence of metabolic muscle disease or genetic polymorphisms. Accordingly, highly individualized and well-timed assessment of the risks and benefits of prescribing potentially myotoxic drugs must be a paramount. Taking into account previous facts, as well as the increasing frequency of reports related to antibiotics–associated myopathies, the aim of this article was to review the current knowledge related to muscular complications associated with use of different antibiotics by adults, including fluoroquinolones, hydroxychloroquine, chloroquine, minocycline, trimethoprim-sulphamethoxazole, isoniazid and daptomycin.
**Introduction**

Owing to its mass, high blood flow, and mitochondrial energy metabolism, the muscle tissue seems particularly susceptible to a drug-related injury (1). Accordingly, many drugs used for therapeutic interventions can cause unanticipated toxicity in muscle tissue, often leading to considerable morbidity, in which a drug-induced, or toxic, myopathy can be defined as the acute or subacute manifestation of myopathic symptoms (1). Drug-related myopathies can vary in their clinical presentations, from mild myalgias with classical features involving muscle weakness, soreness, tenderness, stiffness, cramping, or aching, yet without any elevation in creatine kinase; going through myositis with elevated creatine kinase with or without muscle symptoms, all the way to rhabdomyolysis - the most serious form characterized by severe muscle symptoms and a creatine kinase level 10 times the upper limit of normal or higher (2). Elevated creatine kinase levels are not always sufficient for adequate diagnosis of toxic myopathy, and for the purpose of additional differential diagnosis a biopsy is commonly required. Hence, at the cellular level, drug-associated myopathies most generally result in necrosis, vacuolar changes, or mitochondrial dysfunction. The aim of this article was to provide the current update and to review the muscular complications associated with use of different antibiotics by adults with potential viable implications for practicing physicians.

**Moxifloxacin and other fluoroquinolones**

The fluoroquinolone class of antibiotics is considered to be relatively safe and well tolerated, and they are used to treat a wide range of infections because of their excellent gastrointestinal absorption, superior tissue penetration and broad-spectrum activity (3). Despite their popularity, a number of adverse effects have been attributed to fluoroquinolones, including adverse effects on tendons, cartilage, bone, and muscle (4). Although the etiology of fluoroquinolone-associated muscle disorders has yet to be fully elucidated, evidence supports a relationship with both latent myopathic disorders and the fluorine atom in fluoroquinolones, which is also consistent with the fact that no adverse muscular events have been reported with unfluorinated quinolones (4). Moxifloxacin is a member of the fluoroquinolones with well defined indications for use, including sinusitis, community acquired pneumonia or intraabdominal infections. Although rhabdomyolysis was not at the list of so far reported adverse effects related to moxifloxacin, Sanjith et al. (5) recently reported a case of 75-year-old female with large left cerebellar infarct causing obstructive hydrocephalus,
which required ventriculoperitoneal shunt surgery. However, from the second day she had to be treated against catheter-associated urinary tract infection with intravenous moxifloxacin (400 mg/day). Four days later, serum creatinine increased overnight to 4.5 mg/dl with concomitant hyperkalemia and creatinine phosphokinase levels of 61,000 U/L. An adequate differential diagnosis for rhabdomyolysis was performed, but the moxifloxacin-induced rhabdomyolysis was ultimately proposed. Moxifloxacin was omitted and alkaline diuresis was instituted, which over the next four days resulted in reduction of the serum creatinine and potassium with simultaneous normalization of urine color. Cotrimoxazole was started instead of excluded quinolone antibiotic. The authors have presumed that in this case moxifloxacin-induced rhabdomyolysis could be categorized as a probable one.

In this paragraph some of the most prominent case reports due fluoroquinolone-associated rhabdomyolysis are additionally stated. Hence, a case of fluoroquinolone-associated rhabdomyolysis was connected to gatifloxacin in a 50-year-old male, who was admitted with intermittent fever and lower urinary tract symptoms. The distinctive clinical presentation and temporal association of gatifloxacin with symptoms, biochemistry values and subsequent improvement after withdrawal was indicative for George et al. (6) to suggest that rhabdomyolysis in their patient was gatifloxacin-induced one. Moreover, the early onset of rhabdomyolysis in this patient suggested a direct gatifloxacin effect on muscles and collagen fibers. In accordance, rhabdomyolysis due to levofloxacin was previously reported on a 68-year-old renal transplant patient (7). This was substantiated with the chronological set of events, where rhabdomyolysis developed only after levofloxacin had been added to this patient’s existing medication, with the complete cessation after the exclusion of levofloxacin, despite the renewal of all other potential myotoxic medications. In the similar way, a 19-year-old male patient who developed ofloxacin/levofloxacin-induced rhabdomyolysis during admission for periorbital cellulitis with typical symptoms (myalgia, weakness, and swelling of the arms) and high serum creatine kinase levels (up to 16,546 IU/L) was reported by Hsiao et al. (8). Next, a case of rhabdomyolysis with fatal outcome after a treatment with levofloxacin was described by Petitjeans et al. (9) in a 77-year-old female patient with a background of serious cardio-pulmonary disease who required an oral ambulatory treatment with levofloxacin for pulmonary infection. Finally, Guis et al. (10) reported a case of a 33-year-old man treated with norfloxacin for *Escherichia coli* cystitis. Rhabdomyolysis was detected and it was positively correlated with the occurrence of general muscular fatigue, cramps, tendon disorders, and articular pain. Fifteen days after the treatment
was stopped a slight myalgia persisted with still elevated creatinine phosphokinase activity.

**Hydroxychloroquine and chloroquine**

Hydroxychloroquine is anti-malarial drug, which is also used to treat rheumatoid arthritis and systemic lupus erythematosus, rarely inducing myopathy and sensory neuropathy after long-term use. Consequently, hydroxychloroquine-induced myopathy is generally characterized with proximal weakness, which is mild or moderate, with infrequent serious weakness and respiratory failure (11). Still, after the therapy is discontinued, the resolution of symptoms is slow and may be incomplete (12). Ghosh et al. (13) have recently reported that in a 58-year-old woman with long-standing mixed connective tissue disorder and with proximal leg weakness for 4 months, who was also treated with 400 mg/day of hydroxychloroquine and varying doses of prednisone over 15 years, creatine kinase was found to be 600 U/mL, while magnetic resonance imaging of quadriceps showed edema. A biopsy of frozen sections of the quadriceps muscle revealed myriad acid-phosphatase–positive autophagic vacuoles indicating increased lysosomal activity. The trichrome stain showed numerous fibers harboring single or multiple vacuoles with or without granular material. After discontinuing hydroxychloroquine, there was a gradual improvement in the patient’s weakness. Generally, hydroxychloroquine – related muscle toxicity, although probably more common than what is so far described in the literature (14-20), is often unrecognized and it should be considered with further attention if the patient has a history of hydroxychloroquine use with underlying rheumatologic disease with accompanied evidence of unexplained myopathy such as elevated muscle enzymes, chest pain, generalized or proximal muscle weakness (21). In addition, one should have in mind that the differential diagnosis of vacuoles on light microscopy would include: [1] metabolic - acid maltase deficiency, phosphofructokinase deficiency, carnitine deficiency, periodic paralysis; [2] inflammatory - inclusion body myositis; [3] infectious - echovirus; [4] neurological - Duchenne’s dystrophy, oculopharyngeal dystrophy, and distal myopathy; or [5] toxic - colchicine, hydroxychloroquine, alcohol, glucocorticoids, cyclosporine, as well as any cause of hypokalemia, but also the treatment with vincristine or zidovudine (22).

Chloroquine is another anti-malarial agent with the more pronounced toxic potential than hydroxychloroquine, however with the similar mechanism of toxic action at the level of skeletal muscles, namely lysosomal damage and rimmed vacuole formation after drug accumulation followed by
the cellular enzyme inhibition. Namely, chloroquine, as a lysosomotropic agent, mediates autophagic protein degradation in the autophagic-lysosome system and promotes accumulation of sequestered materials in the autophagosome by terminating protein degradation in the lysosome system (23). A non-specific, mild to moderate, painless proximal muscle weakness in both upper and lower extremities can be usually detected. Posada et al. (24) reported a 59-year-old female with cutaneous discoid lupus and lupus panniculitis treated for seven months with chloroquine (250 mg/day) and prednisone. Because of the incomplete clinical response chloroquine dosage was increased to 250 mg/12 h. Although there was an evident improvement in cutaneous disease, the patient presented progressive proximal muscle weakness on upper and lower extremities during the following seven months. Laboratory tests showed high levels of creatine kinase (218 U/L) and lactate dehydrogenase (544 U/L); while autophagic vacuoles and fibre degeneration with increased acid phosphatase staining related to augmented lysosomal activity was seen after muscle biopsy. An outcome of chloroquine exclusion was characterized by the significant improvement of muscle symptoms and the muscle enzymes normalization. In accordance to the previous pathological finding, a muscle biopsy of the right deltoid in an 89-year-old man with a 3-year history of progressive oropharyngeal dysphagia showed vacuolar changes with prominent increases in lysosomal enzyme activity in both vaculoated and nonvacuolated fibres, being consistent with a toxic myopathy, yet withdrawn after chloroquine was omitted (25).

**Minocycline**

Minocycline is a broad-spectrum antimicrobial agent and a semi-synthetic product of tetracycline, which is widely prescribed for the treatment of severe acne vulgaris (26). However, minocycline is also used in the treatment of rheumatoid arthritis as a disease-modifying drug, wherein it modifies activation of the T-cell response. In the recent case report of Bokuda et al. (12) a 75-year-old woman suffering from rheumatoid arthritis was presented with a myopathy, which predominantly affected her lower limbs. She was unable to perform toe- or heel-walking and there was a mild symmetrical weakness and atrophy in the lower limb muscles. The patient has been continuously treated with minocycline (200 mg/day) for the past 7 years. Hence, histological finding of a biopsied muscle was characterized by scattered atrophic myofibers with rimmed vacuoles enclosing the pigment granules. Additional histochemical staining result was consistent with type II minocycline-induced cutaneous pigmentation, based on the fact that the pigment comprised both
iron and melanin. Finally, autophagic vacuoles that were detected by electron microscopy were constantly observed together with the frequent collections of pigment granules. The authors have concluded that there was a strong association between the finding of autophagic vacuoles and the accumulation of minocycline-induced pigments. This was indicative for the assumption that the long-term minocycline treatment induced pigment accumulation, leading to elevation of autophagic activity and rimmed vacuolar myopathy. The proposed conclusion was also in accordance with the established fact that the rimmed vacuolar myopathy represents a specific category of autophagic vacuolar myopathies, which for example includes a drug-induced autophagic vacuolar myopathy caused for example by hydroxychloroquine (13, 20). A similar case involving prolonged use of minocycline (100 mg/day) for longstanding acne vulgaris in a previously healthy 23-year-old woman who gradually developed progressive proximal limb weakness, severe myalgias exacerbated by exercise, generalized fatigue, arthralgias of the hands and feet, and painful erythematous plaques over her legs with the particular finding of increased serum creatine kinase value of 2,116 IU/L was reported by Geddes et al. (26). A modified Gomori trichrome-stained cryostat section of the left deltoid muscle revealed an inflammatory infiltration of the interfascicular septae with ‘punched-out’ lesions in myofibers corresponding to myofibrillar loss and scattered necrotic fibers undergoing slow phagocytosis. The temporal relationship between the administration of minocycline and the onset of the patient’s symptoms, plus amelioration of symptoms, signs, and laboratory abnormalities after drug withdrawal was established. In conjunction with the latest case reports the association between minocycline administration and the development of acute myopathy and rhabdomyolysis were earlier pointed out by Narvaez et al. (27) and Rahman et al. (28), respectively.

**Trimethoprim-sulphamethoxazole**

Trimethoprim-sulphamethoxazole is commonly used in the prevention and/or treatment of various infections produced by sensitive bacteria. Having in mind that it is also the drug of choice for pneumonia treatment related to *Pneumocystis jirovecii* (previously classified as *Pneumocystis carinii*), trimethoprim-sulphamethoxazole is frequently prescribed to HIV-infected patients with diagnosed pneumocystis pneumonia - the most prevalent opportunistic infection in quoted vulnerable population. Although rhabdomyolysis secondary to trimethoprim-sulphamethoxazole is sporadic, it has the highest frequency of occurrence in immunocompromised male patients with HIV infection (29). In one of the latest reports a case of rhabdomyolysis associated with trimethoprim-sulphamethoxazole in a HIV-
infected patient was presented by Jen and Sharma (30). Namely, a 33-year-old African American man with newly diagnosed AIDS was submitted to the following treatment: combination of efavirenz 600 mg/emtricitabine 200 mg/tenofovir 300 mg once daily; fluconazole 100 mg once daily; azithromycin 1200 mg weekly and trimethoprim-sulphamethoxazole 160 mg/800 mg daily. After two weeks the patient returned to the hospital and was presented with persistent, high-grade fevers, suspected to be trimethoprim-sulphamethoxazole – related one. During the hospitalization the antibiotic was discontinued, but the patient was restarted on trimethoprim-sulphamethoxazole following discharge without the clear rationale, presuming that the details of the patient’s hospital course were not communicated to the outpatient physician. Two days after the follow-up visit, he returned to the emergency room of hospital with severe muscle pain in his upper and lower extremities, acute renal failure and a significantly elevated creatine phosphokinase (31,694 U/L) consistent with rhabdomyolysis. The patient reported that the symptoms developed within hours after he took a single dose of trimethoprim-sulphamethoxazole. The patient gradually improved following discontinuation of trimethoprim-sulphamethoxazole and the supportive care institution. The authors have proposed that based on the temporal relationship between the development of rhabdomyolysis and administration of trimethoprim-sulphamethoxazole, it is very likely that their patient experienced antibiotic-induced rhabdomyolysis, and that described episode of rhabdomyolysis was considered a probable adverse drug reaction associated with trimethoprim-sulphamethoxazole. In accordance to the above described case report, the first report about trimethoprim-sulphamethoxazole – induced rhabdomyolysis in an allogeneic stem cell transplant patient receiving treatment for pneumonia related to *Pneumocystis jirovecii* (31) supports earlier emphasized fact that rhabdomyolysis secondary to trimethoprim-sulphamethoxazole is more frequent in immunocompromised patients.

**Isoniazid**

Isoniazid – associated rhabdomyolysis is identified as uncommon adverse drug reaction. It can be a consequence of extreme muscle force development due to generalized seizures, or direct toxicity on muscles through the generation of reactive oxygen species and lipid-peroxidation products induced either by drug or some of its metabolites. In addition, statistically significant correlations were retrospectively observed for the elevation of creatine phosphokinase muscle fraction with the duration/amount of drug ingested and the frequency of seizure (32). One of
the latest and very interesting reports covering quoted adverse effect of isoniazid, a widely used anti-tuberculosis drug, was presented by Liu et al. (33) in a patient with chronic heart failure. Although this is beyond the primary scope of this manuscript, it has to be underlined that apart from the principal result stating that there was plausible association between isoniazid treatment and rhabdomyolysis, this case has also raised the possibility that there might be a link between an end-stage dilated cardiomyopathy and rhabdomyolysis, having in mind that sizeable peripheral modifications actually do occur in the skeletal muscle of patients with chronic heart failure. Thus, a 56-year-old Chinese man had been treated for chronic decompensated heart failure for 8 years. His basic medications included hydrochlorothiazide (or furosemide), spironolactone, digoxin, metoprolol, perindopril (later switched to losartan). During the course of treatment he suffered from breast cancer, which required a radical mastectomy and the omission of spironolactone. Afterward, he was diagnosed with type 2 diabetes mellitus and initiated treatment with gliclazide and acarbose. Finally, at the year eight of treatment he was diagnosed with pulmonary tuberculosis localized in the right upper lobe, which was apart from the ordinary specimen-dependent diagnostic procedures also confirmed by chest X-ray and CT scan. Standard anti-tuberculosis protocol was instituted (isoniazid 300 mg/d, ethambutol 750 mg/d, and streptomycin i.m. 750 mg/d). Two months later cardiac resynchronization was attempted with implantation of a biventricular pacemaker. At the admission a moderate tenderness and myalgias on palpation of the muscles of the calves, thighs, right shoulder girdle, biceps and triceps were noted. The serum values of creatine phosphokinase, CK-MB, myoglobin were significantly increased (14 781 U/L, 98 U/L, 3000 microg/L, respectively), yet with no evidence of autoimmune myopathy at immunological screening. Additional differential diagnostic procedures were performed and isoniazid-induced rhabdomyolysis was ultimately suspected. Isoniazid was discontinued, which was accompanied with intravenous hydration with isotonic crystalloid. The alkalization of urine was administered and the management of heart failure was continued. Although myalgias gradually diminished with concomitant reduction of serum creatine phosphokinase, myoglobin and liver function test values, the patient died due to progressive deterioration of heart failure.

Daptomycin

Daptomycin belongs to a cyclic lipopeptides class of bactericidal antibiotics with a strong activity against Gram-positive pathogens, wherein the clinically most relevant bacteria would include coagulase-positive and
coagulase-negative staphylococci, as well as streptococci and enterococci (34). This antibiotic is approved for the complicated skin and skin structure infections treatment due to sensitive bacteria and the treatment of S. aureus bloodstream infections, including those caused by methicillin-susceptible and methicillin-resistant S. aureus (35). The use of daptomycin has been associated with an elevation in creatine phosphokinase level, and earlier published case reports have documented the presence of myopathy in patients who received this antibiotic, as well (35-37). Although rhabdomyolysis is a rare adverse effect reported with daptomycin use, one of the latest cases regarding rhabdomyolysis associated with the co-administration of daptomycin and pegylated interferon α-2b with ribavirin in a patient with hepatitis C was reported by Colomba et al. (38). The patient had a history of intravenous drug abuse and hepatitis C, and was admitted to hospital because of fever and pain in the right gluteal region, which was associated with the presence of a gluteal abscess. During the last five months the patient was treated with pegylated interferon α-2b and ribavirin without reporting any side effect. Empirical antibiotic therapy with levofloxacin (750 mg once daily i.v.) and piperacillin/ tazobactam (4.5 g every 6 h i.v.) was instituted, but due to lack of clinical improvement levofloxacin was switched to daptomycin (500 mg/day i.v.). The second dose was administered, by mistake, 4 h before it should have been. Soon after, the patient suddenly complained of weakness and diffuse aches in the proximal thighs and arms that were accompanied with very high serum creatinine phosphokinase levels (12933 U/L). Suspecting daptomycin-induced rhabdomyolysis, treatment was switched to linezolid and meropenem, with concomitant hydration (2 L/day) to preserve the renal function. The creatinine phosphokinase level slowly decreased during the next 10 days after omission of daptomycin. Although there were several possible causes of rhabdomyolysis to consider in this case, daptomycin was clearly identified as the most likely cause, given the temporal relationship between elevation of creatine phosphokinase level and drug administration.

Conclusions

In patients with possible and suspecting drug-induced myopathy, assessing the risks and benefits of prescribed therapy is pivotal. In that way, the relationship between the muscle disorder and the specific drug can be suggested if pre-existing muscular symptoms and other causes for the myopathy were initially absent, also if the presence of a reasonable temporal relationship between the start of treatment or change of dose and the appearance of symptoms can be established with partial or complete
resolution of symptoms after the drug is withdrawn, and finally if the following patient’s factors that increase the risk of drug induced myotoxicity would be properly considered: advanced age (> 70 years), administration of multiple myotoxic drugs, high doses of myotoxic drugs, female gender, thyroid disease, existing hepatic or renal disease, surgery (perioperative period), existence of metabolic muscle disease or genetic polymorphisms (39). In accordance, a clinical approach to patients with possible antibiotic-evoked muscle toxicity should always include an assessment of risk factors and physical findings, with vigilant consideration of alternate diagnoses. Moreover, the ultimate determination about continuation of particular antibiotic treatment should depend on the estimated balance between the expected benefit of antibiotic therapy for each patient individually, and the probability that the symptoms are actually due to antibiotic action.

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References


