Malignant Hyperthermia Susceptibility Revealed by Myalgia and Rhabdomyolysis During Fluoroquinolone Treatment

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ABSTRACT. Fluoroquinolones cause myalgia, but this complication is not clearly documented. We describe a patient who developed myalgia and rhabdomyolysis during fluoroquinolone treatment. The patient was a 33-year-old man treated with norfloxacin for common cystitis. He complained of general muscular fatigue, tendon disorders, and articular pain during treatment. When the antimicrobial agent was stopped, symptoms decreased, with persistence of slight myalgia for 10 days. Rhabdomyolysis was detected. Six months later, investigation by 31P magnetic resonance spectroscopy revealed an oxidative disorder and an abnormal abundance of phosphomonoesters. In vitro contracture tests led to a diagnosis of malignant hyperthermia susceptibility. Our case shows that for any subject presenting myalgia with rhabdomyolysis triggered by fluoroquinolone treatment, the presence of a latent myopathy should be investigated. (J Rheumatol 2001;28:1405–6)

Key Indexing Terms: MALIGNANT HYPERTHERMIA  FLUOROQUINOLONE  RHABDOMYOLYSIS

Rheumatologists frequently evaluate patients with muscle pain and elevated creatine phosphokinase (CPK). In some cases, these signs indicate a susceptibility to malignant hyperthermia with potentially adverse consequences.

We describe a patient who developed severe myalgia and rhabdomyolysis during fluoroquinolone treatment, with a moderate rise in temperature. These symptoms slowly disappeared when treatment was discontinued. A malignant hyperthermia susceptibility1 was suspected and investigated. Fluoroquinolones are known for their adverse effects on the musculoskeletal system, especially tendons in adults2–4. Also, in about 1% of cases, these antibiotic agents cause myalgia. In contrast to tendinopathies, this complication has not been clearly documented, and no detailed observation with a complete muscle investigation has been reported.

CASE REPORT

The patient was a 33-year-old man who was not under any treatment. He suffered from Escherichia coli cystitis and, for the first time, received Noroxine® (norfloxacin) 800 mg/day for 10 days. His history was unremarkable except for moderate swelling of calves after strenuous muscular effort. There was no family history of muscular pathology, disease of the immune system, or any serious adverse response to anesthesia. He complained of general muscular fatigue and cramps, and tendinous and articular pain on the third day of treatment. Myalgia worsened and on the 7th day he was bedridden. He noted his urine was dark. At this time (10th day) fluoroquinolone was stopped. Over the subsequent 2 weeks, symptoms decreased while slight myalgia persisted. After 2 more weeks, blood tests showed normal blood count, urea, electrolytes, and calcium. Thyroid function was normal.

Testing for specific antibodies (Jo-1) of inflammatory myopathy was negative. Fifteen days after treatment was stopped, CPK activity was elevated (1000 IU/l vs normal 24–195 IU/l). Activities of serum aspartate and alanine aminotransferases and serum lactate dehydrogenase were also raised. All viral hepatitis serologies were negative.

Six months after all clinical symptoms and biochemical anomalies had disappeared, his forearm muscles were investigated by 31P magnetic resonance spectroscopy (MRS). Metabolic indices measured during normoxic exercise were normal, but ischemic exercise revealed a moderate oxidative disorder and an abnormal abundance of phosphomonoesters, indicating compensating glycolytic activation. This result was confirmed by bicycle ergometer test showing CPK increase at rest and, at the 10th minute, a moderate increase in potassium and ammonia in the blood. Because of these anomalies, a muscle biopsy was performed. Histological examination showed only a type II fiber atrophy. In vitro contracture tests in the presence of halothane or caffeine according to the European Malignant

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Hyperthermia Group protocol\textsuperscript{6} were positive for halothane (0.7 g at 2\%) and for caffeine (0.8 g at 2 mM) and established a diagnosis of malignant hyperthermia susceptibility.

**DISCUSSION**

Our observation shows that norfloxacin induced severe myalgia and rhabdomyolysis in a patient susceptible to malignant hyperthermia. The myopathic syndrome was clearly related to the drug exposure and an intrinsic predisposition to development of malignant hyperthermia. This pharmacogenetic myopathy is often latent, with diverse clinical symptoms. A hypermetabolic state is usually observed in response to the administration of halogenated anesthetics, but unspecific symptoms not related to anesthetics, such as heat stroke, rhabdomyolysis, chronically raised serum CK, and myalgia, can be observed in malignant hyperthermia susceptible patients. There are clinical and physiological clues pointing to a similar muscle deficit, accounting for susceptibility to malignant hyperthermia and rhabdomyolysis induced by this fluoroquinolone. Both situations are triggered by fluorine-containing compounds. The possible role of fluorine in this fluoroquinolone induced rhabdomyolysis is supported by the observation that no muscular adverse effects have been reported during treatment by unfluorinated quinolones, which were widely used in the past. In muscle physiology, the fluoride ion plays a role in Ca\textsuperscript{2+} dependent K\textsuperscript{+} channels, and probably in calcium release channels (ryanodine receptor)\textsuperscript{7} that are known to be affected in the skeletal muscles of malignant hyperthermia susceptible subjects. K\textsuperscript{+} efflux and increased intracellular Ca\textsuperscript{2+} levels are observed in experimental models when fluoride ions interact with calcium receptors.

Our case suggests that malignant hyperthermia susceptibility should be investigated in subjects who develop myalgia during fluoroquinolone treatment. We propose to use a protocol similar to the one we apply for malignant hyperthermia\textsuperscript{5}. Noninvasive investigation of muscle metabolism is initially conducted by \textsuperscript{31}P MRS. If metabolic disorders are observed (100% sensitivity), a muscle biopsy for histoenzymology and contracture tests is performed.

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**REFERENCES**