Clarithromycin-induced rhabdomyolysis: a case report

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Abstract: Rhabdomyolysis is a clinical and laboratory syndrome that is caused by various etiologies, involving the skeletal muscle. Clarithromycin, like other macrolides, is an inhibitor of CYP450 3A4, the major enzyme responsible for the metabolism of several drugs, in particular some statins. Rhabdomyolysis related to macrolide–statin interaction has previously been described. To date, rhabdomyolysis induced by clarithromycin has been described in only one previous report. We describe the case of a 90-year-old Caucasian male, admitted to the University Hospital of Pisa for dyspnea, who developed rhabdomyolysis associated with clarithromycin administration.

Keywords: clarithromycin, rhabdomyolysis, pneumonia

Introduction
Adverse drug reactions (ADRs), including interactions, in older people are a common cause of admission to hospital and are also a common cause of disease in hospitalized patients. Frail elderly patients appear to be particularly at risk of ADRs. In some cases, this is because insufficient account is taken of the effect of age and frailty on the pharmacokinetic and pharmacodynamic of the drug, especially in relation to hepatic and renal elimination. Although many ADRs are recognized during the drug development process and before licensing, this is not always the case, especially when they are uncommon or rare. Moreover, patients with severe cognitive impairment may not be able to refer symptoms related to an ADR, making the recognition of this clinical condition a medical problem.

Rhabdomyolysis is a clinical and laboratory syndrome that is caused by various etiologies, involving the skeletal muscle. Rhabdomyolysis is characterized by the leaking of myoglobin and other intracellular proteins and electrolytes into the circulation, and may be associated with a wide variety of diseases, injuries, medications, and toxins. It is important to recognize drug-induced rhabdomyolysis because clinical effects are usually reversible. Rhabdomyolysis related to macrolide–statin interaction has previously been described. Clarithromycin, like other macrolides, is an inhibitor of CYP450 3A4, the major enzyme responsible for the metabolism of several drugs, in particular some statins like simvastatin and atorvastatin. To date, rhabdomyolysis related to clarithromycin has been reported in only one previous case report. We report the case of a 90-year-old Caucasian male, admitted to the University Hospital of Pisa for dyspnea, who experienced rhabdomyolysis related to clarithromycin treatment.
**Case report**

A 90-year-old Caucasian male was admitted to the University Hospital of Pisa for dyspnea. He had experienced dyspnea for 2 weeks, and showed signs of pneumonia after a chest X-ray was performed. The patient was affected by Alzheimer’s disease, in advanced phase, and did not take any home-medications as referred by his general physician. At admission in the emergency room, clinical workup revealed mental confusion (the relatives referred progressive cognitive impairment for several months), sinus tachycardia (115 beats per minute), basilar wheezes, and rhonchi. Body temperature was 36.6°C with normal systemic blood pressure (140/80 mmHg), diuresis, and blood oxygen saturation (SO₂ 96.2%). Routine laboratory exams, including complete blood cell count, thyroid hormones, liver (aspartate aminotransferase and alanine aminotransferase) and muscle (creatine kinase [CK]) enzymes, as well as the coagulation pattern, resulted within normal limits. Serum brain natriuretic peptide was measured and a cardiac markers’ curve (including myoglobin) was also started, ruling out cardiogenic dyspnea. Blood potassium and creatinine concentrations were 4.96 mEq/L (reference range 3.5–5 mEq/L) and 122.8 µmol/L (reference range 45–90 µmol/L), respectively.

At the emergency room, a diagnosis of acquired pneumonia was made and treatment with ceftriaxone (1 g four times daily, intravenous), hydration (crystalloid 1.5 L/day), aerosol with salbutamol and oxitropium, O₂ inhalation (3 L/minute), and dalteparin (2500 UI, subcutaneous) was started. After the geriatric ward admission, clarithromycin (500 mg two times daily, intravenous) was also started. On the second day of hospitalization, for continuing sinus tachycardia, in the absence of any evident causes (fever, hypotension, arterial-venous fistula, thyrotoxicosis, suspected drug treatments, etc) beta-blocker treatment (bisoprolol 1.25 mg, daily) was added and a cardiac markers’ curve was restarted (Figure 1). The second point of the curve, almost 6 hours after the third clarithromycin dose, revealed a huge myoglobin increase (1144 ng/mL; 8.5 times the upper normal range [28–138 ng/mL]) without electrocardiogram modifications. Serum CK was then measured, resulting markedly elevated (1100 U/L; 6.5 times the upper normal range [38–180 U/L]) along with a mild creatinine increase (152.9 µmol/L), in the absence of liver enzyme alterations (aspartate aminotransferase, alanine aminotransferase). Urine color concomitantly changed toward dark brown and hemogasanalysis revealed a slight respiratory insufficiency type I with normal pH. A diagnosis of rhabdomyolysis was made and clarithromycin was stopped, while the concomitant therapy with ceftriaxone, bisoprolol, and aerosol with salbutamol and oxitropium was continued. The patient was immediately treated with intravenous crystalloid hypotonic solution (80 mL/hour) and corticosteroid (40 mg methylprednisolone, intravenous). Serum CK and myoglobin levels decreased within a few days and a chest X-ray showed significant improvement. The patient was discharged home on the sixth hospital day (Figure 1) with the diagnosis of iatrogenic rhabdomyolysis and acquired pneumonia of unknown etiology. Indeed, serum and urinary antigen and antibody exams excluded the presence of Legionella pneumophila, Streptococcus pneumoniae, and Mycoplasma pneumoniae while virus infection assessments were not performed.

**Discussion**

Clarithromycin, like other macrolides, is an inhibitor of CYP450 3A4, the major enzyme responsible for the metabolism of several drugs, in particular some statins as simvastatin and atorvastatin.3,6–9 Rhabdomyolysis related to macrolide and statins interaction has previously been described; however, rhabdomyolysis related to clarithromycin has been reported in only one previous case report.6,10 In our case, there was an evident temporal sequence between clarithromycin exposure-withdrawal and the onset-recovery from rhabdomyolysis biochemical signs, while other potential causes of muscle damage were reasonably excluded. Accordingly, the Naranjo probability scale confirmed a probable relationship (score 6/9).11

![Figure 1](image-url)
A general physician and a nurse followed the patient at home, thus we are confident the home care was carried out in a correct manner, ruling out mistakes and accidental drug intake. Moreover, an interaction with other concomitant medications was improbable considering the rapid resolution after clarithromycin withdrawal and the elimination pathways of the concomitant drugs (both bisoprolol and ceftriaxone have hepatic and renal elimination routes).\textsuperscript{11,12} In addition, bisoprolol was administered at the minimal dose (1.25 mg) and both bisoprolol and ceftriaxone, as single therapy, were never related to an adverse drug reaction like rhabdomyolysis.

We ruled out infection as the possible cause of muscle damage considering the sequence of the events. In fact, the patient was admitted to the hospital for dyspnea developed at home since 2 weeks, while serum CK suddenly increased 2 days after hospital admission. If rhabdomyolysis had been caused by the infection we would have expected that serum CK increased earlier, thus being already evident at hospital admission. Moreover, the most common rhabdomyolysis-associated bacterial infections were ruled out by specific tests.

The diagnosis of rhabdomyolysis, unless there is a high index of suspicion, can be missed since muscular pain, swelling, and tenderness may not be prominent or even absent. The definitive diagnosis should be made by laboratory tests including serum CK and urine myoglobin.\textsuperscript{5} In our case, the patient had advanced cognitive impairment making him unable to easily refer any symptom, and the diagnosis was made by the huge elevation of biochemical markers (6.5 times the upper normal value for CK, 8.5 times for myoglobin). Overall, these findings allowed us to make the diagnosis of rhabdomyolysis with sufficient warranty. Although clarithromycin associated rhabdomyolysis is mainly due to pharmacokinetic interactions, a direct muscle toxicity might be postulated.\textsuperscript{3,10}

Disclosure
The author reports no conflicts of interest in this work.

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