CASE REPORT

Rhabdomyolysis Following a Short Course of Clarithromycin

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A healthy 5-year-old girl developed myalgia and an elevated creatine kinase concentration after 4 days of normal doses of clarithromycin. Myalgias resolved and creatine kinase values returned to normal following discontinuation of clarithromycin. No other precipitating factors or interacting drugs were identified; hence, clarithromycin was suspected as the cause of the rhabdomyolysis.

INDEX TERMS adverse drug event, clarithromycin, pediatric, rhabdomyolysis

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INTRODUCTION

Rhabdomyolysis is a rare but potentially life-threatening syndrome that results from an acute breakdown of skeletal muscle fibers.¹ Injury to myocytes results in both clinical symptoms and biochemical findings. All cases of rhabdomyolysis are associated with an elevation in serum creatine kinase, which is the most sensitive confirmatory laboratory test for rhabdomyolysis. Clinical presentation is variable and ranges from asymptomatic disease, to widespread or generalized muscle weakness and Coca-Cola-colored urine, to a life-threatening condition associated with electrolyte imbalances (e.g., hyperkalemia), acute renal failure, and disseminated intravascular coagulation.^{1,2}

There are multiple physical and nonphysical causes of rhabdomyolysis, including alcohol, illicit drugs, toxins, immobility, infections, injuries, metabolic disorders, seizures, and overexertion. The most common cause of rhabdomyolysis in adults is medication. Hydroxymethylglutaryl coenzyme A reductase inhibitors (i.e., statins) have been widely implicated, especially in combination with medications that interfere with statin metabolism. Although etiologic data are lacking in the pediatric population, the largest case series showed that viral myositis is the most common underlying cause of rhabdomyolysis in children. The rates of acute renal failure due to rhabdomyolysis are lower in children than in adults.³

CASE REPORT

A healthy, Asian-American, 5-year-old, 21.8-kg girl presented to the urgent care clinic with a fever of 102°F and a 5-day history of productive cough. The child completed a course of azithromycin for febrile illness prior to the visit. She received age-appropriate doses for a total of 600 mg of azithromycin during 5 days. Upon physical examination, a diagnosis of pneumonia was established. The patient was then prescribed clarithromycin 125 mg twice daily (12 mg/kg/day) for 10 days. Four days later the child began to complain of leg pain, with an absence of any other symptoms. Her fever had resolved. That same day the child was brought back to the urgent care clinic, where a creatine kinase concentration of 949 U/L (normal range, 2–177 U/L) was discovered. No other laboratory tests were ordered. The child had normal muscle strength and reflexes, with mild tenderness bilaterally over the calf muscles. Clarithromycin was immediately stopped and no new antibiotics were initiated. Creatine kinase concentrations gradually decreased, and the patient's muscle strength improved. Four days later creatine kinase returned to 125 U/L and the child no longer complained of leg pain. Because she was not taking any other medications, clarithromycin was thought to be the precipitating factor for rhabdomyolysis. A score of 5 was determined using the Naranjo adverse drug reactions probability scale; thus, clarithromycin can be considered a *probable* cause of rhabdomyolysis in this patient.⁴

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DISCUSSION

To date, only one other report identified in the literature details the development of rhabdomyolysis after monotherapy with clarithromycin.⁵ In that report, a 45-year-old African American male was treated with 500 mg of clarithromycin orally twice daily for 10 days. He began to experience diffuse muscle pain and weakness 6 days into the therapy. Based on symptomology and laboratory values, such as urine myoglobin 450 ng/mL (normal, <5 ng/mL), creatine kinase 550 international units per liter (normal range, 38-174 international units per liter), and aspartate aminotransferase 1000 U/L (range, 5-35 U/L), he was diagnosed with severe rhabdomyolysis. The patient denied using any other prescription, herbal, or illicit medications. As in our pediatric patient, his rhabdomyolysis resolved after discontinuation of macrolide.

Documented cases of rhabdomyolysis in patients taking clarithromycin involved drug interactions with statins through inhibition of CYP450 enzyme system. Clarithromycin is a macrolide antibiotic indicated for a variety of infections. It has a spectrum of activity similar to erythromycin. Like other macrolides, it is bacteriostatic and exerts its action by binding to the subunit 50S of the bacterial ribosome and peptide translation. It is a strong inhibitor of the CYP450 enzyme system.⁶ In particular, clarithromycin interferes with CYP3A4 enzyme and can inhibit its own metabolism.⁷ Differences in the allelic frequencies of CYP3A isoenzymes between Asians and whites have been reported; however, there is no consistent evidence from studies that show how this influences drug metabolism.^{8,9} We did not identify any literature describing the differences in the metabolism of macrolides between various ethnic populations. The child did not have any family history or other risk factors, such as repeated exertion, starvation, or concomitant medications, that predispose someone to the development of rhabdomyolysis. However, because the child has Asian ancestry, a possibility of increased drug exposure cannot be ruled out.

As reported previously, viral infections are a common cause of rhabdomyolysis in children. The symptoms of viral myositis are nonspecific, and the pediatric patient may lack the classic triad of symptoms seen in adults with rhabdomyolysis, mainly myalgia, changes in urine color, and creatine kinase elevation. Thus, we cannot conclusively rule out viral myositis as the cause of rhabdomyolysis in this patient.

Of interest, prior to the start of clarithromycin therapy the child was treated with a 5-day course of azithromycin, another potent macrolide. Perhaps it

is the combined duration of therapy with macrolides that predisposed the child to the development of rhabdomyolysis. Regardless, the chronologic relationship between the appearance of myalgia and the start of clarithromycin led us to conclude that clarithromycin is the responsible agent in this case.

CONCLUSION

We reported a probable case of rhabdomyolysis due to clarithromycin. Although there have been few isolated cases of rhabdomyolysis with the use of macrolides, and the mechanism of action behind this adverse drug reaction is not understood, clinicians need to be aware of this potential adverse drug reaction and stay vigilant, especially in patients at risk for rhabdomyolysis.

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