



Treatment of Clarithromycin-Induced Rhabdomyolysis with Continuous Renal Replacement Therapy

Klaritromisine İkincil Gelişen Rabdomyolizin Sürekli Renal Replasman ile Tedavisi

Klaritromisine İkincil Gelişen Rabdomyoliz / Clarithromycin-Induced Rhabdomyolysis

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Özet

Rabdomyoliz yaygın ve şiddetli kas yaralanması ile karakterize nadir görülen, hayatı tehdit eden bir hastalıktır. Rabdomyolizin kliniği asemptomatik hastalıktan akut böbrek yetmezliği gelişimine kadar değişkenlik göstermektedir. Sık kullanılan makrolid grubu bir antibiyotik olan klaritromisin sitokrom p 450 enzim sistemini inhibe ederek rabdomyolize neden olabilir. Erişkinlerde makrolit ve statinlerin birlikte kullanımı sonrası rabdomyoliz gelişimi bildirilmiştir. Ama çocuklarda özellikle de tek başına klaritromisin kullanımı sonucu nadir görülmektedir. Bu yazıda 8 yaşında bir hastada klaritromisin kullanımını takiben gelişen ağır rabdomyoliz ve akut böbrek yetersizliği ile ilgili deneyimimizi sunmaktayız.

Anahtar Kelimeler

Rabdomyoliz; Klaritromisin; Renal Replasman

Abstract

Rhabdomyolysis is a rare, life-threatening syndrome characterized by a diffuse and severe muscle injury. Clinical presentation is variable, ranging from asymptomatic disease to acute renal failure. Clarithromycin, a commonly used macrolide antibiotic, can cause rhabdomyolysis by inhibiting CYP450 enzyme system. Rhabdomyolysis related to combination of macrolide and statins has been previously reported in adults. However, it is rare in children, especially with clarithromycin monotherapy. Herein we report our experience with a severe rhabdomyolysis and acute renal failure following clarithromycin administration in a 8-year-old patient.

Keywords

Rhabdomyolysis; Clarithromycin; Renal Replacement

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Introduction

Rhabdomyolysis is a clinical and laboratory syndrome caused by myocyte necrosis that impairs the integrity of the cell membrane and leads to the release of myoglobin and toxic intracellular constituents containing electrolytes and proteins into the bloodstream [1]. Assessment of serum creatine kinase is the most sensitive confirmatory laboratory test. Rhabdomyolysis may be associated with toxins, crush injury, overexertion, seizures, genetic disorders, and metabolic disorders. The most common cause of rhabdomyolysis in children is viral myositis, whereas medications in adults [2]. It is important to recognize drug induced rhabdomyolysis early because it is usually reversible. Rhabdomyolysis secondary to concomitant use of macrolides and statins has been reported previously in adult [3], but it is uncommon in children, especially in clarithromycin monotherapy [2]. We report the successful treatment of rhabdomyolysis and acute renal failure related to administration of clarithromycin with continuous veno-venous hemodialysis therapy in a 8-year-old boy. Clarithromycin was suspected to be the cause of rhabdomyolysis, as no other precipitating factor or drug interaction were identified.

Case Report

A 8-year-old previously healthy boy was referred for diffuse and severe muscle pain, weakness and dark urine. He had been administered clarithromycin twice daily (15 mg/kg/day) for 5 days due to fever, cough and rhinorrhea. His muscle pain had started after the second day of clarithromycin. He did not have any concomitant medication. Physical examination revealed a body temperature of 36.60C, heart rate 142 beats/min, arterial blood pressure 115/72 mmHg, and blood oxygen saturation 96%. Muscle strength was 3/5 in all extremities and deep tendon reflexes were hypoactive. Laboratory studies showed creatine kinase (CK) 58722 U/L (normal range, 55-170 U/L), lactate dehydrogenase 4271 U/L, alanine aminotransferase 1435 U/L, aspartate amino transferase >10000 U/L, glucose 89 mg/dl, urea 85 mg/dl, creatinine 1.9 mg/dl, uric acid 8.9 mg/dl, sodium 142 mmol/L, potassium 6.5 meq/L, calcium 6.1 mg/dl, phosphorus 7.2 mg/dl and blood pH 7.34, base excess -11,2 mmol/L, HCO₃ 14,5 mmol/L, pCO₂ 27,4 mmHg and thyroid-stimulating hormone 2.2 mIU/mL. Urine output was diminished. It was brown in colour and myoglobin was detected. There was no calculi and its culture was sterile. Complete blood count, peripheral blood smear and other serum electrolyte tests were all in normal ranges. Serum lactate, pyruvate, ammonia, tandem mass spectroscopic analysis and urine organic acids levels were all normal. Influenza A (H1N1) or other respiratory tract viruses were not detected in nasopharyngeal swab by rRT-PCR assay. Serologic studies determined Epstein-Barr immunoglobulin M (IgM), herpes simplex virus IgM, cytomegalovirus IgM and mycoplasma IgM as negative. The probability that the symptoms of rhabdomyolysis that occurred after clarithromycin treatment were an adverse drug reaction (ADR) was assessed using the Naranjo ADR probability scale. The total Naranjo score for the patient was 5, which is in the "probable" range. So, clarithromycin was considered a probable cause of rhabdomyolysis and was immediately stopped. Aggressive intravenous hydration was initiated. Because of impaired renal function, (and) high

potassium and phosphorus levels and fluid overload, the patient received continuous veno-venous hemodialysis (CVVHD) with a dialysate flow rate of 900 mL/hour, in which multibic O was used. The blood flow rate was 90 mL/min. After 3 days of treatment, by recovery of renal function and electrolyte imbalance, urine output improved and CVVHD was stopped.

Discussion

Clarithromycin, like the other macrolides inhibits CYP450 enzyme system. Clarithromycin is also involved in the CYP3A4 component of this pathway which is responsible for statins and its own metabolism. Beside pharmacokinetic interactions clarithromycin might cause direct muscle toxicity [3]. Rhabdomyolysis due to interaction of macrolides and statins is reported in adults [3]. To date, there are only two pediatric cases in the literature reporting rhabdomyolysis after monotherapy with clarithromycin [2,4].

The infections, especially acute viral infections, metabolic disorders, seizures, immobility and drugs can lead to rhabdomyolysis. Viral myositis is the most common cause of rhabdomyolysis in children [2]. The symptoms of viral myositis are nonspecific and child may not have the classic symptoms of rhabdomyolysis. Therefore we cannot completely rule out viral infections in our patients, although viral markers are negative. An objective causality assessment using the Naranjo probability scale suggested that clarithromycin was the probable cause of rhabdomyolysis in our patient [5].

Rhabdomyolysis ranges from asymptomatic elevation of muscle enzymes to acute renal failure (ARF) due to obstruction of renal tubules with myoglobin. Acute renal failure is the most serious complication of rhabdomyolysis. The rate of ARF due to rhabdomyolysis is lower in children compared with adults. Wu et al reported the prevalence of ARF as 5% among 191 children and only 3 of them required renal replacement therapy (RRT) [6].

Although there is not a definite correlation between elevated serum CK levels and rate of ARF, high CK levels can suggest the severity of rhabdomyolysis. In a recent study, it is reported that if a peak value of CK >5000 U/L the risk of ARF increases and if a peak value of CK >10 000 U/L the probability of RRT increases [7].

For the recovery of renal function, complete removal of myoglobin from circulation is required. Continuous veno-venous hemodialysis (CVVHD) is more effective than hemodialysis in reducing serum myoglobin levels [8]. We used CVVHD in the treatment of acute renal failure in our patient and after hemodialysis for 3 days he completely recovered. The two other reported pediatric cases after clarithromycin usage improved only with intravenous fluid and drug withdrawal. None of them had acute renal failure and received CVVHD. Our patient may be the only pediatric case who had get CVVHD for severe rhabdomyolysis after clarithromycin administration.

In conclusion, it is important for clinicians to recognize rhabdomyolysis early in patients treated with clarithromycin because the clinical process due to drugs is usually reversible. We reported this case both to remind clinicians to be aware of this adverse effect of clarithromycin which is commonly used in daily practice and also to consider continuous renal replacement treatment as a remedy of rhabdomyolysis.

Competing interests

The authors declare that they have no competing interests.

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