CASE REPORT

Dose-independent daptomycin associated rhabdomyolysis: Case report

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ABSTRACT

Background: Administration of Daptomycin may be associated with elevation in creatinine phosphokinase (CPK) level and increased risk of rhabdomyolysis with or without acute renal failure with a reported incidence of 2.8% in phase III clinical trials.

Case Presentation: We report the case of 70 years old male patient who had chronic vertebral osteomyelitis based on tissue (bone) culture, lumber spine MRI and abdominal CT. Daptomycin was started at a dose of 6 mg/kg intravenously once daily and continued at home thru Home Health Care (HHC) with baseline CPK=40 IU/L. After six days of treatment, CPK level elevated to 1254 IU/L. Despite initial improvement in CPK with reduction of Daptomycin dose, patient had to be re hospitalized again after 12 days of discharge with CPK level=15825 IU/L and acute kidney injury.

Conclusion: Daptomycin can be associated with elevations in CPK level and rhabdomyolysis despite reduction of dose. A baseline CPK level before starting Daptomycin treatment and more frequent monitoring in patients with additional risks, including renal impairment, is recommended.

Key words: Daptomycin; Rhabdomyolysis; Creatinine phosphokinase

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INTRODUCTION

Rhabdomyolysis is a disorder of skeletal muscle breakdown with presence of muscle contents leakage, is often complemented by myoglobinuria. In severe cases, acute renal failure with potentially life-threatening metabolic imbalances may result. Rhabdomyolysis is an uncommon serious adverse effect reported with Daptomycin use [1]. CPK is the recommended marker to monitor probable rhabdomyolysis during Daptomycin therapy [2]. Most reported cases mentioned the onset of symptoms and CPK elevation to occur seven to ten days of starting medication [3]. Nevertheless, there are many reported cases showed early onset muscle pain with CPK elevations after two to three doses. [4]. Daptomycin is a member of cyclic lipopeptide antibiotics, which was approved by Food and Drug Administration on 12 September, 2003 for the treatment of complicated skin and skin-structure infections used in the treatment of systemic and life-threatening infections caused by Gram-positive micro-organisms including methicillin-resistant *Staphylococcus aureus,* methicillin-resistant *Staphylococcus epidermidis,* vancomycin-resistant Enterococcus species, and penicillin-resistant Streptococcus pneumoniae. Its distinct mechanism of action makes it useful in treating infections caused by multiple drug-resistant bacteria. Daptomycin binds to the cell membrane of susceptible microorganism and causes rapid depolarization, inhibiting intracellular synthesis of DNA, RNA and protein. Dapromycin is bactericidal and concentration dependent antibiotic. We report the case of an elderly patient who developed severe rhabdomyolysis after administration of Daptomycin. A Naranjo score was calculated and linked to a possible classification for Daptomycin induced rhabdomyolysis [5].

CASE PRESENTATION

A 70 years old male patient known case of type-2 diabetes mellitus, hypertension, and diastolic dysfunction with ejection fraction 58% came to emergency department complaining of right upper quadrant and epigastric pain plus vomiting for 2 weeks along with right middle finger pain which was previously diagnosed with severe cellulitis attributed to his uncontrolled diabetes. He was febrile with a temperature of 39.5°C. Blood culture grew Methicillin sensitive Staphylococcus aurous (MSSA). Abdominal Computed tomography (CT) and lumber spine magnetic resonance imaging (MRI) showed L4-L5 lumbar spine osteomyelitis and para-spinal collection. Patient was admitted as a case of multifocal bacteremia due to lumbar spine osteomyelitis with para-spinal collection, Right middle finger wound and chest infection. Patient started on ciprofloxacin 400 mg every 12 hours in combination with cloxacillin 2 g every 4 hours. Fluconazole 400 mg every 24 hours was added later after laminectomy and evacuation of epidural abscess and debridement, as recommended by neurosurgery team as MRI showed no improvement after evacuation. After 84 days of previously mentioned antibiotics regimen, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and patient symptoms showed slow interval improvement. In order to facilitate home intravenous antibiotic therapy with a less frequent dosing regimen, treatment was changed to Daptomycin 6 mg/kg once daily plus same previous doses of fluconazole and ciprofloxacin. Baseline CPK level was within normal range (40 IU/L), patient received the first dose of Daptomycin at hospital without adverse reaction. Patient was discharged home

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to continue intravenous antibiotics at home through home health care team. Weekly lab draw was arranged to monitor CPK, CBC, renal function, and inflammatory markers. After six days of Daptomycin treatment, CPK level started to elevate to 1254 IU/L, then dose was decreased to 4 mg/kg instead of 6 mg/kg and the next CPK level after 4 days decreased to 662 IU/L (Table 1, Figure 1). Medication profile was checked to rule out causes of drug induced rhabdomyolysis. During that time, patient was on the following listed medications: ciprofloxacin, fluconazole, senna, lactulose, insulin and enoxaparin. None of the above-mentioned medications were associated with CPK elevation. Therefore, a clear relationship between daptomycin initiation and CPK level elevation was identified and prompted its discontinuation. The patient rough to emergency department with history of slurred speech with intermitted confusion for 3 days. It was associated with history of generalized weakness and decrease in his usual activity, along with decrease oral intake and muscle pain. Patient was admitted as a case of Daptomycin-induced rhabdomyolysis with CPK level (16687 IU/L), and acute kidney injury with electrolytes disturbance (hypercalcemia, hypokalemia, and hypomagnesemia). Daptomycin was stopped and the patient was returned to the previous Antibiotics regimen (Cloxacillin, Ciprofloxacin and Fluconazole). Patient received total of 3 Liters of normal saline bolus over 3 hours at the time of admission then continued on continuous infusion at rate of 100 ml/hr. In the second day, patient shifted to dextrose 5% normal saline continuous infusion at rate of 80 ml/hr because of poor oral intake and low blood sugar readings. CPK level and overall clinical condition improved gradually over 8 days, reaching normal level.

Table 1: CPK level elevation Vs daptomycin doses.

	CPK	Daptomycin dose
Base line	94	Off daptomycin
Day 1		(6 mg/kg) 450 mg
Day 2		(6 mg/kg) 450 mg
Day 3		(6 mg/kg) 450 mg
Day4		(6 mg/kg) 450 mg
Day 5		(6 mg/kg) 450 mg
Day 6	1254	(4 mg/kg) 300 mg
Day 7	662	(4 mg/kg) 300 mg
Day 8	15825	(4 mg/kg) 300 mg
Day 9	16687	Daptomycin discontinued
Day 13	942	Off daptomycin
Day 15	180	Off daptomycin
Day 17	94	Off daptomycin

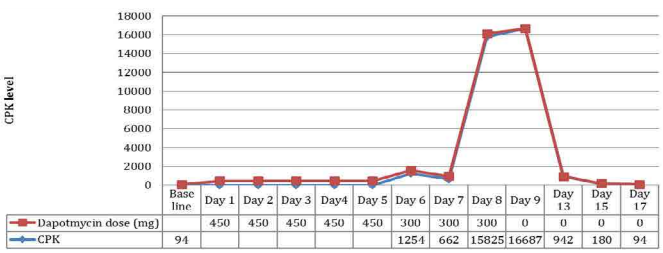

Figure 1: Daptomycin doses Vs CPK level.

DISCUSSION

Daptomycin induced rhabdomyolysis is a known possible complication and warrants high level of awareness due to life-threatening potential. Frequent monitoring of CPK is necessary for early diagnosis of such complication. Safety and efficacy of Daptomycin was evaluated by Arbiet et al, by comparing Daptomycin with Vancomycin or Piperacillin/Tazobactam in two randomized trials [1]. They concluded that Daptomycin at dose 4 mg/kg once daily is safe and effective as standard therapy for the treatment of complicated skin and skin-structure infections. Kazory et al, reported a case of generalized muscular weakness followed by non-oliguric acute renal failure with elevated liver enzymes after administration of 6 mg/kg once daily Daptomycin for 10 days [6]. CPK elevation was extremely high, presenting with severe myopathy [6]. Another study reported by Sbrana et al, administered Daptomycin at a dose of 6 mg/kg twice daily [7]. After 9 days, patient developed myopathy with elevated CPK. This case concluded that dosages above 8 mg/kg and an interval shorter than once daily markedly enhanced the risk for rhabdomyolysis. One case was reported by Felipe et al, in 2011 about Daptomycin re-challenge therapy after episode of rhabdomyolysis with concomitant administration of statin [8]. Daptomycin was re-administrated at 6 mg/kg once daily with absence of statin therapy and was continued successfully for 18 days until the course of therapy was complete with no repeated episode of muscle toxicity. As our case reveals, reducing Daptomycin dose did initially provide improvement in CPK levels, but shortly thereafter remained a risk for subsequent CPK elevation and development of rhabdomyolysis. Therefore, a reduction of Daptomycin dosing may provide an initial false sense of assurance in avoiding and managing CPK elevation complication. Daptomycin should be administered as once daily dose, due to severe adverse effects were observed more frequently if infusions were administered more frequently, such as every 8 or 12 hours. A once-daily Daptomycin therapy regimen is supported by its concentration-dependent activity. The pharmacokinetic/pharmacodynamic indices that correlate with Daptomycin activity are the ratios of C max to MIC and 24-hour AUC to MIC. Administration of once daily dose of Daptomycin is recommended in outpatient parenteral antibiotic therapy, as was done in our case. Dosing is performed according to body weight that ranged from 4 to 6 mg/kg and should be adjusted in impaired renal function patients [9]. Finally, frequent monitoring and raised alertness of such adverse effect need to be present throughout the course of Daptomycin administration, irrespective of any dose-related variation or improvement of CPK levels. Greater than once-daily dosing and co-administration of drugs that cause myopathy, rhabdomyolysis or CPK elevation are important factors involved in Daptomycin-induced rhabdomyolysis. One case was reported by Felipe et al. in 2011 about Daptomycin re-challenge therapy after episode of rhabdomyolysis with concomitant administration of statin [8]. Daptomycin was re-administrated at 6 mg/kg once daily with absence of statin therapy and was continued successfully for 18

days until the course of therapy was complete with no repeated episode of muscle toxicity.

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