A case report and literature review of daptomycin-induced liver injury

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\textbf{ABSTRACT}
Daptomycin is a lipopeptide antimicrobial used to treat gram positive organisms including multi-drug resistant infections. It has been shown to occasionally cause abnormalities in liver function but more commonly is associated with elevations in serum creatinine phosphokinase (CK) (Hair and Keam, 2007) [1]. We describe a case where a patient being treated for methicillin-resistant \textit{Staphylococcus aureus} (MRSA) bacteremia with daptomycin developed asymptomatic elevated transaminases without evidence of multiorgan failure, hyperbilirubinemia or elevation of CK levels. Other etiologies for liver injury were considered and ruled out, and after daptomycin was discontinued, the transaminases returned to normal levels. We also provide a review of other cases to date documenting possible cases of daptomycin-induced liver injury.

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\section*{Introduction}
Drug-induced liver injury (DILI) is associated with over 1000 herbal products and drugs in therapeutic doses [2]. Although the incidence of DILI is low (1/10,000–100,000), about 1/7 cases of acute hepatic failure is due to an adverse drug reaction and DILI has recently become the leading cause of urgent liver transplantation. DILI is also the most common adverse event that leads to withdrawal of a drug from the market and discontinuation of a clinical trial [2].

Daptomycin, a lipopeptide bactericidal antimicrobial with broad gram positive coverage including resistant organisms such as vancomycin-resistant enterococci (VRE), MRSA, glycopeptidemEDIATELY SUSCEPTIBLE \textit{Staphylococcus aureus}, coagulase-negative staphylococci and penicillin-resistant \textit{Streptococcus pneumoniae} [3,4], is a drug that has been found to cause DILI in a small number of cases. According to initial clinical trials done with daptomycin, DILI was documented in 3\% of all participants [5] without concordant increases in gamma-glutamyl transferase (GGT) levels [6]. Initial clinical trials with daptomycin revealed that higher doses (8 mg/kg/day) compared to standard doses (6 mg/kg/day) resulted in reversible adverse skeletal muscle effects [4].

Daptomycin-induced myopathy has been described as a skeletal-muscle specific myopathy characterized by minimal degeneration and inflammation. The degeneration is usually readily reversible and does not result in fibrosis, which distinguishes it from inflammatory myopathies (significant inflammation and fibrosis), congenital myopathies (alteration of skeletal muscle) and rhabdomyolysis (diffuse muscle necrosis and kidney failure) [7]. The marker used for daptomycin-induced myopathy has been serum CK. Serum CK activity has been shown to be a sensitive marker of skeletal muscle damage, however, in the case of daptomycin toxicity, has not been found to be related to cardiac or brain tissue damage [1,7]. The mechanism of CK release form myocytes has been hypothesized as mediated by membrane perturbations given daptomycin’s lipophilic characteristics, antimicrobial mechanism of action and inability to cross cell membranes [7].

To our knowledge, there have been no reported cases of daptomycin-induced hepatotoxicity in the absence of hyperbilirubinemia, renal failure and CK abnormalities. Six other case reports of daptomycin-induced hepatotoxicity have been published on patients without pre-existing liver disease [6,8–12]. All cases tested CK and transaminase levels while the patients were on daptomycin therapy. In most of these cases, transaminase levels returned to normal about one to two weeks after discontinuation of daptomycin (Table 1). Based on the available data, there are no discernible trends in transaminase elevation, the role of pre-existing liver disease if any or pattern of liver. We will now present a case report followed by a review of previous case reports.

\section*{Case report}
Our case patient had a past medical history of insulin dependent diabetes mellitus complicated by neuropathy and

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The Naranjo probability scale is one of the scales used to establish causality in DILI along with other scales such as the RUCAM/CIOMS and Maria & Victorino scales but currently none are considered the gold standard [14]. Our patient’s Naranjo score falls into the “probable” category. This indicates that there is a probable relationship between hepatotoxicity and daptomycin therapy in our patient, given the temporal relationship without an alternative explanation for DILI in this patient. RUCAM scores fell into the “highly probable” range and M&V scores resulted in a “possible” association [15].

Similar to the Bohm report, our case involves daptomycin-induced hepatotoxicity in the absence of CK elevation, AKI, myositis and in contrast to the Bohm report, normal levels of bilirubin [6]. Thus, there are four case reports so far which identify daptomycin-induced liver toxicity in the absence of rhabdomyolysis and of those, only one without hyperbilirubinemia. This indicates that there is an alternative mechanism for daptomycin-related liver injury. To our knowledge this has not been described at the cellular level and it is unknown whether or not daptomycin has direct hepatocellular cytotoxic effects.
Review of previous cases involving DILI from presumed daptomycin use

Echevarria et al. described the first case report of DILI secondary to daptomycin use associated with rhabdomyolysis. They present a case of gram positive osteomyelitis initially treated with vancomycin later switched to daptomycin due to an allergic reaction [16]. Daptomycin was started at 500 mg daily, and the patient’s baseline CK was 102 U/L with normal transaminase levels. Of note the patient was also on a statin initially; this was discontinued with the start of daptomycin therapy. On day nine of treatment, the patient developed diffuse muscle pain and weakness. Physical exam findings included no sensory or neurological deficits however, decreased strength was present in both upper (4/5) and lower (3/5) extremities. Lab work at this time revealed a CK of 20,771 U/L and aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels of 239/48 U/L respectively. Daptomycin was discontinued at this point and the patient was admitted to the intensive care unit for close monitoring. The patient experienced resolution of pain and recovery of strength within 48 h and was discharged on linezolid with close CK monitoring. The patient’s CK and symptoms normalized two weeks later. The patient had a normal creatinine throughout this course [16].

Echevarria et al. also describe recent animal studies with daptomycin where skeletal muscle toxicity in dogs was found to be closely related to the frequency of daptomycin dosing [16]. This study found that smaller doses of daptomycin every eight hours resulted in more skeletal muscle toxicity and CK elevations than single daily dosing [7]. Furthermore, Oleson et al. did not see a relationship between CK elevations or myopathy and increased serum daptomycin concentrations. However, based on the Echevarria et al. case report and the other cases reported thus far, once daily dosing may not be protective for all patients. Furthermore, clinical trial data does not suggest that concomitant statin use increases the risk of daptomycin-induced myopathy [5]. Thus Echevarria et al. concluded that the damage most likely occurred through direct hepatotoxicity [16].

Kazory et al. in 2006 reported the first case of daptomycin-induced liver and kidney injury in the presence of rhabdomyolysis. The case involved osteosclerotic which was initially treated with vancomycin, voriconazole and levofloxacin [9]. After eight weeks of therapy, a bone biopsy revealed Torulopsis glabrata, VRE and MRSA. At that time the patient was started on daptomycin 6 mg/kg/day. Ten days into the treatment course with daptomycin, the patient experienced generalized muscle weakness leading to immobilization as well as non-oliguric AKI. Creatinine levels went from a baseline of 0.9 mg/dL to 2.7 mg/dL, CK levels were found to be 21,243 U/L and AST/ALT levels were also elevated at 375/219 U/L respectively. Daptomycin was discontinued at that time and the patient was treated with intravenous fluids resulting in resolution of muscular symptoms as well as normalization of renal function, CK and transaminase levels. In this case the authors concluded that the AKI and other abnormalities were caused by rhabdomyolysis secondary to daptomycin use [9]. There was no other potential source of rhabdomyolysis in this patient and this is the first case report documenting concomitant renal injury as well as DILI secondary to daptomycin administration.

Another case reported in 2007 similarly found elevations in CK as well as transaminase levels with significant muscle weakness after daptomycin initiation after only three days of treatment [10]. This case involved a patient with multiple comorbidities found to have VRE bacteraemia started on daptomycin 5 mg/kg/day. At that time lab testing revealed CK of 29,234 U/L and an AST/ALT levels of 1153/332 U/L respectively. Daptomycin was stopped and seven days later; transaminase levels began to trend down and CK levels were down to 290 U/L. The authors calculated a Naranjo score which resulted in a “probable” classification regarding the correlation of daptomycin and DILI in this case [10]. Other cases of daptomycin-induced myopathy have also described elevations in CK levels after only a few doses [17]. The authors of this report point out that daptomycin is excreted by the kidneys and has to be adjusted for creatinine clearance. In their patient, who was a renal transplant recipient with a concomitant history of polymyalgia rheumatica, the authors hypothesized that these factors may have predisposed this patient to daptomycin-induced muscle toxicity [10].

In 2008, Abraham et al. reported the first case of daptomycin-associated acute hepatic and renal toxicity in the absence of elevated CK levels and rhabdomyolysis [8]. In this case, the patient was initially started on daptomycin 4 mg/kg/day five weeks prior to presentation for presumed osteomyelitis with a history of VRE urinary tract infection and MRSA sacral wound cultures. Symptoms on presentation were progressive fatigue and nausea. Admission testing revealed an increase in serum creatinine levels from a baseline of 0.9 mg/dL to 2.9 mg/dL, an AST/ALT of 6,020/8,050 U/L (baseline was normal), an elevated alkaline phosphatase at 370 U/L and total bilirubin at 2.0 mg/dL. Interestingly, this patient’s CK level was within normal limits at 111 U/L, the patient was not septic, and no liver or kidney abnormalities were seen on computed tomography of the abdomen and pelvis. Upon admission, the patient’s medications were all discontinued including daptomycin, which was replaced with vancomycin and ciprofloxacin. Viral hepatitis serologies were also negative. The patient was hydrated and serial liver function testing revealed decreasing transaminase levels. Six weeks after discharge, serum creatinine levels had come down to 1.4 mg/dL and AST/ALT were 51/81 U/L respectively. The authors concluded that daptomycin may cause DILI without elevations in CK, as in this case the patient had not been on any new medications and had not been found to have other reasons for liver injury [8].

In 2012, a report by Colomba et al. involved a case of rhabdomyolysis with co-administration of daptomycin and pegylated interferon alpha-2b and ribavirin [18]. This patient had a history of intravenous drug abuse and Hepatitis C and was admitted with a gluteal abscess after five months of interferon/ribavirin treatment. The patient was started empirically on daptomycin 500 mg/day 48 h into admission as fever were not improving on levofloxacin and piperacillin-tazobactam. Prior to daptomycin, the patient’s CK was slightly elevated at 518 U/L, creatinine was 1.6 mg/dL, transaminase levels were normal and Hepatitis C viral load was undetectable. After two doses of daptomycin, the patient developed weakness and diffuse extremity pain, CK levels at that time were found to be 12,933 U/L and AST/ALT 371/67 U/L. A urine drug screen was negative, blood cultures were positive for MRSA and suspecting daptomycin involvement in rhabdomyolysis, the patient was switched to linezolid. This patient’s CK and transaminase levels continued to increase for another six days and the CK did not start coming down until ten days after daptomycin was discontinued. The authors concluded that daptomycin was likely the cause of this patient’s acute rhabdomyolysis and transaminase elevation [18].

In 2014, Bohm et al. reported the first case of DILI secondary to daptomycin treatment in which the only abnormality was an elevation in transaminase levels without concomitant AKI, CK elevation or symptoms of myositis [6]. The patient was found with MRSA bacteremia, an abscess in the left antecubital fossa as well as tricuspid valve endocarditis. The patient was placed on 6.9 mg/kg/ day of daptomycin and six days later was found to have significantly elevated transaminase levels including GGT and bilirubin. The patient’s creatinine remained at baseline and CK levels at that time were 43 U/L. An infectious and autoimmune hepatitis workup and imaging of the liver did not reveal any underlying liver disease. The patient’s other medications were also
thoroughly reviewed for hepatic toxicity resulting in discontinuation of a few (senna, dicyclomine). As the patient only had elevations in transaminase levels and no evidence of rhabdomyolysis, daptomycin was continued. At that time the patient's transaminase levels continued to rise and the gastroenterology service was consulted. The teams agreed that daptomycin-induced hepatotoxicity was the most likely reason for the patient's rise in transaminase levels. Daptomycin was thus discontinued after thirteen total days of treatment which resulted in a decline in transaminase levels. Bohm et al. suggest that in this case the liver function test pattern was consistent with a mixed hepatocellular and cholestatic liver injury with daptomycin-induced liver injury as the "probable" cause according to the Naranjo scale [6].

The Bohm report also included a single-center retrospective cohort analysis of all cases of daptomycin use and DILI between 2008-2013. Out of 759 cases of daptomycin use, nine were identified with ALT elevations, ten with total bilirubin elevations, and five with both ALT and total bilirubin elevations. All cases had suspected etiologies for transaminase elevations other than daptomycin use and chart review was consisted with the noted etiologies. None of the cases found were consistent with daptomycin-induced hepatotoxicity [6].

A case in 2014 by King et al. describes a patient who presented with osteomyelitis of the right foot and after fourteen days of daptomycin developed rhabdomyolysis. DILI and AKI [11]. This patient was initially admitted with an elevated creatinine to 1.4 mg/dL and a baseline CK of 49 U/L. After six days of inpatient vancomycin, the patient was discharged home on daptomycin 6 mg/kg/day and oral ciprofloxacin, with a discharge creatinine of 1.4 mg/dL. Of note, this patient had a history of hypertension and diabetes mellitus (type 2) and was on metformin at home, but not on a statin. Nine days later, the patient presented to the hospital with body aches and extremity pain, bloodwork was notable for a creatinine of 1.19 mg/dL, and the patient was sent home with a diagnosis of a viral-like illness. The patient returned to the hospital two more times with worsening symptoms, however a CK level was not checked during the first two encounters. On the patient's third presentation, the creatinine level was found to be 4.7 mg/dL, potassium 6 mmol/L, CK 16,710, AST/ALT 750/236 U/L and bilirubin was normal. At that time daptomycin was discontinued and the patient's CK peaked at > 20,000 (fourteen days into daptomycin therapy), and decreased to 7467 U/ml at discharge, symptoms also resolved with cessation of daptomycin. According to Naranjo score, this patient had a “probable” adverse drug reaction and the authors concluded that daptomycin was the likely cause [11].

Most recently, a case published in 2016 presented a patient with a complex medical history who was being treated for MRSA endocarditis with daptomycin 7 mg/kg/day [12]. The patient had been receiving daptomycin for three weeks prior to presentation, and was admitted septic with jaundice, scleral icterus, elevated AST/ALT (1331/1449 U/L), total bilirubin 5.8 mg/dL, lactic acidosis, hypercoagulable state and heart failure. The patient underwent a workup for acute liver failure and daptomycin was stopped on admission. The patient was treated supportivey and diagnosed with a urinary tract infection which was treated with meropenem. Laboratory testing continued to improve throughout admission. The authors believe that the liver injury was likely a combination of hepatic congestion secondary to heart failure as well as DILI secondary to daptomycin use. Using the Naranjo score, this case was a “probable” association with liver injury and daptomycin use [12].

Conclusion

In conclusion, we report the first case of daptomycin therapy related DILI in a patient (without pre-existing liver disease) with no evidence of hyperbilirubinemia, concomitant CK abnormalities, rhabdomyolysis or AKI. We also present a review of all previous cases that describe daptomycin-related DILI. Interestingly, each case varies significantly from the next and it is difficult to draw a common conclusion as to the pattern and form of daptomycin related DILI. Based on the available reports, the onset of daptomycin-related DILI may occur anywhere between two to fourteen days after initiation of therapy and is readily reversible with the cessation of daptomycin, without long term sequelae. Elevated transaminases were noted to resolve in about one to two weeks from daptomycin discontinuation in most cases. Unfortunately, we do not have pathologic data from these cases and cannot make any direct conclusions as to how daptomycin is causing DILI. However, based on available lab data from these cases it appears to more often favor a hepatocellular pattern of liver injury rather than a mixed hepatocellular/cholestatic or cholestatic type of liver injury. It also remains unclear to what extent prior liver disease contributes to acquiring DILI secondary to daptomycin use.

Although daptomycin-induced myopathy has been well described in the literature, daptomycin continues to appear to be a rare cause of DILI, especially in the absence of rhabdomyolysis. Evidence suggests that daily dosing results in lower rates of myopathy and CK elevations. However, serum CK elevations have not been found to be associated with increased serum daptomycin concentrations [7], which suggests that other factors may predispose certain patients over others to daptomycin-induced myopathy. As noted, daptomycin related DILI, although rare and not readily predictable, is a potentially serious side effect if not identified and addressed early. Hence, clinicians should be aware of these possible adverse effects and use appropriate clinical monitoring of CK, and case by case monitoring of liver function tests in patients on daptomycin therapy.

Conflicts of interest

None to declare.

Author contributions

AJ wrote the manuscript and was involved in data acquisition and analysis. MRDJ was involved in reviewing and editing the manuscript. Both authors were involved in conceptualization of the manuscript.

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