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Rhabdomyolysis associated with the co-administration of daptomycin and pegylated interferon α -2b and ribavirin in a patient with hepatitis C

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Sir,
Rhabdomyolysis is a rare adverse effect reported with daptomycin use. Here we report the first case of creatinine phosphokinase (CPK) elevation with rhabdomyolysis developing during the co-administration of daptomycin and pegylated interferon α -2b and ribavirin.

We describe the case of a patient with a history of intravenous drug abuse and hepatitis C admitted to our division because of fever and pain in the right gluteal region.

The patient's general condition was poor, but his physical examination was unremarkable, except for the presence of a right gluteal abscess. The patient had been taking pegylated interferon α -2b and ribavirin for 5 months without reporting side effects. On admission, liver function tests were within normal limits, serum CPK level was slightly elevated (518 U/L; normal values 39–308 U/L), lactate dehydrogenase (LDH) was 580 U/L (normal values 240–480 U/L), serum creatinine was 1.6 mg/dL and estimated CL_{CR} was 124.8 mL/min. The white blood cell (WBC) count showed neutrophil leucocytosis (WBC 11 580 cells/mm³, 87.1% neutrophils) and a low platelet count (72 000 cells/mm³). All other laboratory findings were within normal limits. Hepatitis C virus (HCV) RNA viral load was undetectable. Blood cultures were performed.

The patient was started on empirical antibiotic therapy with levofloxacin (750 mg once daily intravenously) and piperacillin/tazobactam (4.5 g every 6 h intravenously). Due to lack of improvement of symptoms and fever after 48 h, levofloxacin was switched to daptomycin (500 mg daily intravenously). The second dose was administered, by mistake, 4 h before it should have been. Five days after admission, after only two doses of daptomycin, the patient suddenly complained of weakness and diffuse aches in the proximal thighs and arms. Serum CPK levels were very high (12 933 U/L) and further elevations in aspartate aminotransferase (AST) and alanine aminotransferase (ALT), 371 and 67 IU/L, respectively, were also noted. A urine

drug screen was performed to rule out damage related to illicit substance use, and the results were negative. Blood cultures were positive for methicillin-resistant *Staphylococcus aureus* (MRSA). Suspecting daptomycin-induced rhabdomyolysis, treatment was switched to linezolid (600 mg twice daily intravenously) and meropenem (1 g every 8 h intravenously). The patient was hydrated (2 L/day) to preserve renal function, and this was strictly monitored throughout the course; urinalysis was positive for myoglobin. Although daptomycin had been interrupted, CPK levels and AST/ALT levels continued to increase for 5 days after and on the sixth day the CPK level was 45 257 U/L, LDH was 6892 U/L and AST/ALT was 980/107 IU/L. The CPK level slowly decreased 10 days after discontinuation of daptomycin.

Daptomycin is a lipopeptide antibiotic approved for the treatment of complicated skin and soft-tissue infections caused by susceptible Gram-positive strains, including MRSA and vancomycin-susceptible *Enterococcus faecalis*. Daptomycin has also been approved for *S. aureus* bloodstream infection and for the treatment of right-sided endocarditis caused by methicillin-susceptible *S. aureus* and MRSA. The main side effect is skeletal muscle toxicity. In clinical trials, 2.8% of subjects experienced elevations in CPK level, and 0.2% of the study population reported myopathy.¹ This condition is favoured in obesity, diabetes mellitus, chronic renal failure, bacterial sepsis, electrolyte abnormalities and concomitant treatment with statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors).²

Few cases of daptomycin-induced rhabdomyolysis have been described in the literature.^{2,3} Only two reports described patients with early onset rhabdomyolysis related to daptomycin use.⁴ Here, we report the second case of onset after only two doses of daptomycin, with a CPK level of 45 257 U/L. To our knowledge, this is the first case of daptomycin-induced rhabdomyolysis in a patient receiving pegylated interferon α -2b and ribavirin for HCV-related hepatitis. Interferon α -2b, but not ribavirin, has been associated with rhabdomyolysis.⁵ Our patient already had increased CPK levels at presentation, but had never had any sign or symptom of myopathy, suggesting that hepatitis C therapy had been well tolerated. Thus, daptomycin was administered despite increased CPK levels. We believe that a prominent role in daptomycin toxicity was played by the short interval between the two doses (by mistake); according to the literature, dosing frequency seems to have a more direct effect upon skeletal muscle than peak plasma concentration.^{6,7} Our patient also had MRSA bacteraemia. Bacterial sepsis has been associated with the development of rhabdomyolysis, and in this case it may have functioned as a predisposing factor.

In conclusion, given the temporal relationship between daptomycin initiation and elevation in CPK level, we identified daptomycin as the main cause of the patient's myopathy. Therefore, we recommend close monitoring of CPK and symptoms of myopathy in all patients started on this drug. Moreover, we think that the concomitant use of pegylated interferon α -2b most likely induced the adverse activity of daptomycin. It may be advisable, given the limited experience, to interrupt therapy with interferon during daptomycin treatment.

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This study was carried out as part of our routine work.

Transparency declarations

None to declare.

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Unexpected atazanavir-associated biliary lithiasis in an HIV-infected patient

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Sir,

Atazanavir is a widely used protease inhibitor with a favourable pharmacokinetic profile, allowing once-daily dosing with or without ritonavir boosting. It is both a substrate and a competitive inhibitor of cytochrome P450 3A4 and also a competitive inhibitor of the bilirubin-conjugating enzyme UDP glucuronyl

transferase 1A1. Atazanavir is metabolized and eliminated primarily by the liver and its metabolites are excreted in the bile. In healthy subjects, renal elimination of unchanged atazanavir was only 7% of the administered daily dose. A population pharmacokinetic sub-study, derived from study AI424007 in naive patients receiving 200, 400 or 500 mg of atazanavir once daily (a clinical Phase III trial of atazanavir efficacy, safety and tolerability), demonstrated the relationship between plasma exposure (area under the curve and trough plasma concentration) and both safety (hyperbilirubinaemia) and viral efficacy.¹ Renal lithiasis is a commonly reported side effect of atazanavir, with at least 30 cases identified by the FDA between 2002 and 2007.² One case of choledocholithiasis-associated atazanavir in a 47-year-old HIV-infected African female 6 weeks after the initiation of an atazanavir-containing regimen has been published recently.³ Six additional cases of cholelithiasis occurring within months to years after initiation of atazanavir are recorded in the French National Pharmacovigilance Database. A cholecystectomy was performed in four of these cases and atazanavir was identified in biliary stones in two cases. Here we report a new case. The patient signed a written informed consent for publication.

A 64-year-old HIV-1-infected male who was immunovirologically stable (plasma HIV-1 RNA <20 copies/mL and CD4 cells ~525/mm³; CD4 cells=33% of white blood cells) and showed good treatment adherence was hospitalized in July 2010 for exploration of a right flank pain experienced for several months. Ultrasonography revealed a huge gallstone (weight ~13 g, diameter ~25 mm), which was subsequently extracted from the common bile duct by laparoscopic cholecystectomy. After solubilization of the stone in acid aqueous solvent, the brown-coloured solution obtained was analysed to determine antiretroviral drug concentrations using ultra-performance liquid chromatography-mass spectrometry/mass spectrometry.⁴ The atazanavir concentration determined in the gallstone recovered from this patient, who had switched from atazanavir/ritonavir to a darunavir/ritonavir + tenofovir/emtricitabine (300/200 mg once daily)-containing regimen 1 year previously, was approximately 6.0 mg/g. In the same sample, darunavir and ritonavir concentrations were 0.9 and 0.13 mg/g, respectively, while neither tenofovir nor emtricitabine was found. Since 1993, this patient had received 19 successive antiretroviral regimens, including six protease inhibitors, seven nucleoside reverse transcriptase inhibitors and two non-nucleoside reverse transcriptase inhibitors in combination. He had no history of opportunistic infection, and liver and renal functions were normal. The plasma viral load was undetectable for the last 9 years except for two treatment interruptions. Cumulative durations of protease inhibitor therapies were approximately 5 years for indinavir and 5 years for atazanavir. One year after starting unboosted indinavir, the patient developed a nephrolithiasis that resolved completely on switching 800 mg of indinavir three times daily to indinavir/ritonavir (400/100 mg twice daily), leading to a lower indinavir peak plasma concentration and adequate hydration.

Follow-up parameters [median (interquartile range; number of samples)] collected during the last 41 months were as follows: atazanavir plasma concentration at 24 h, ~502 ng/mL (330–631; 8); tenofovir plasma concentration at 24 h, ~53 ng/mL (49–68; 8); variability of atazanavir and tenofovir plasma concentrations at 24 h, ~16% and 21%, respectively; estimated glomerular filtration rate (according to the Cockcroft–Gault equation),