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CORRESPONDENCE

Daptomycin-associated myopathy induced by concomitant administration of mirabegron

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To the Editor,

Daptomycin (DAP) belongs to a new class of antibiotics and possesses bactericidal activity against Gram-positive organisms [1]. Currently, this agent is recommended for the treatment of methicillin-resistant *Staphylococcus aureus* infections and frequently used in various clinical settings [2]. Muscle toxicity is one of the common adverse drug events associated with DAP administration. Incidence rates of myopathy and rhabdomyolysis among patients receiving DAP are estimated about 2–14% and < 5%, respectively [3]. Coadministration of statin [3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors] and antihistamine with DAP is an independent risk factor for the development of DAP-associated myopathy [3]. However, effects of other drugs are still unknown. We describe a first case of DAP-associated myopathy, which was induced by the concomitant administration of mirabegron.

A 57-year-old woman (body weight, 70.8 kg) developed a high fever without remarkable symptoms after left ventricular assist device implantation and aortic valve closure using a bovine pericardial patch for the treatment of acromegalic cardiomyopathy. We detected methicillin-resistant *Staphylococcus epidermidis* in two sets of blood culture examinations, and an investigation by cardiac ultrasonography revealed a vegetation sized 6 × 25 mm at the operated aortic valve. Following a diagnosis of prosthetic valve endocarditis caused by *S. epidermidis*, the patient underwent a re-surgery for aortic valve closure and was administered DAP for 8 weeks (525 mg/day for the first 2 weeks and 525 mg/48 h for the remaining period) because of impaired renal function (serum creatinine level, 1.3 mg/dL; eGFR, 30–35 mL/min/1.73 m^2). There were no adverse drug events during the 8 weeks of treatment at that time.

At 4 weeks following DAP therapy, the patient developed a high fever again and *S. epidermidis* was repeatedly isolated from blood samples. Her renal function remained unchanged, and we re-administered DAP with the same dose and regimen (525 mg/48 h) for the treatment of recurrent endocarditis. Starting 2 days after DAP re-administration, she complained of bilateral stiff shoulders. The patient denied any preceding histories of traumatic events. Laboratory analysis revealed an elevated level of serum creatinine phosphokinase (CPK 440 U/L; normal range 54–286 U/L) on the 4th day of DAP treatment. On the 7th day of DAP treatment, the serum CPK level further elevated to 1051 U/L, and we discontinued the DAP treatment. Subsequently, her muscular symptoms ameliorated and the serum CPK level decreased to a value within the normal range promptly.

We could not understand the reason for the occurrence of myopathy that developed only during the second DAP treatment in spite of the same regimen and renal function; therefore, we reviewed her drug history. Consequently, we found that mirabegron administration for overactive bladder had been incidentally initiated 3 days before DAP re-administration. There was no other change in the drugs that were administered. Although mirabegron administration was continued throughout the course of DAP re-administration, and her myopathy resolved by discontinuation of DAP alone. Based on the above-mentioned findings, we concluded that the muscle toxicity was induced by the combination of DAP and mirabegron in this case. Alternatively, we administered vancomycin for 6 weeks, which yielded a satisfactory outcome.

Mirabegron is a selective beta 3-adrenoceptor agonist, which was approved by the US Food and Drug Administration in 2012 for the treatment of overactive bladder [4]. According to a recent meta-analysis [5], mirabegron may

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increase the risks of hypertension and cardiac arrhythmia; however, the possibility of muscle toxicity development was not investigated. The Japanese package insert does mention the possibility of an increase in serum CPK levels at an incidence of 1–5%. To our knowledge, no previous study has reported a case of DAP-associated muscle toxicity that was induced by the coadministration of mirabegron. However, the clinical course of the patient was suggestive of a drug–drug interaction between DAP and mirabegron that potentially resulted in muscle toxicity. Mirabegron, as well as statins, is metabolized by cytochrome P450 enzymes, mainly CYP3A4, in the liver, while DAP does not undergo hepatic metabolism. Thus, metabolic pathways of the two drugs are different, and the development of myopathy was assumed to be an additive effect of muscle toxicity. In these aging societies worldwide, an increasing number of people experience overactive bladder and undergo treatment with mirabegron. The concomitant administration of these drugs needs further study.

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Compliance with ethical standards

Conflict of interest The authors confirm that there are no conflicts of interests to declare.

Informed consent Informed consent was obtained from the patient.

References

1. Heidary M, Khosravi AD, Khoshnood S, Nasiri MJ, Soleimani S, Goudarzi M. Daptomycin J Antimicrob Chemother. 2018;73:1–11.
2. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. Clin Infect Dis. 2011;52:e18–55.
3. Dare RK, Tewell C, Harris B, Wright PW, Van Driest SL, Farber-Eger E, et al. Effect of statin coadministration on the risk of daptomycin-associated myopathy. Clin Infect Dis. 2018. https://doi.org/10.1093/cid/ciy287.
4. Tyagi P, Tyagi V. Mirabegron, a β3-adrenoceptor agonist for the potential treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder. IDrugs. 2010;13:713–22.
5. Sebastianelli A, Russo GI, Kaplan SA, McVary KT, Moncada I, Gravas S, et al. Systematic review and meta-analysis on the efficacy and tolerability of mirabegron for the treatment of storage lower urinary tract symptoms/overactive bladder: comparison with placebo and tolterodine. Int J Urol. 2018;25:196–205.