Farmacia HOSPITALARIA
Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

CLINICAL CASE
Bilingual edition English/Spanish

Daptomycin associated myoclonus: A case report

Mioclonías por daptomicina: Descripción de un caso

Mariano José Scolari[1], Débora Pellegrini[2]

[1]Servicio de Farmacia, Hospital Británico de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina. [2]Servicio de Clínica Médica, Hospital Británico de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina.

Author of correspondence
Mariano José Scolari
Perdriel, 74
Ciudad Autónoma de Buenos Aires
(C1280AEB). Argentina.
Email:
marianojscolari@gmail.com

Received 3 August 2021;
Accepted 4 October 2021.
Early Access date (11/21/2021).
DOI: 10.7399/fh.11799

How to cite this paper
Scolari MJ, Pellegrini D. Daptomycin associated myoclonus: A case report. Farm Hosp. 2022;46(1):40-2.

Introduction

Daptomycin is a cyclic lipopeptide antibiotic with bactericidal activity that was discovered in 1986 from *Streptomyces roseosporus*[1]. It has been shown to be effective in the treatment of right-sided infective endocarditis and skin infections caused by gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA)[2,3].

Tolerance to daptomycin is usually acceptable and the most frequent adverse effects are elevated creatine phosphokinase (CPK), myalgia, rhabdomyolysis, and gastrointestinal symptoms[3]. However, evidence is scarce on daptomycin-associated neurotoxicity.

We describe the case of a male patient who presented with daptomycin-associated resting myoclonus.

Case description

An 80-year-old man with a history of hypertension, insulin-dependent type-2 diabetes mellitus with multiple target organ damage (ischemic heart disease, chronic kidney failure, and ophthalmoplegia due to third right cranial pair palsy), atrial fibrillation, prostate adenocarcinoma controlled with hormone therapy, and permanent VVI pacemaker due to sinus node disease. He had no history of medication allergies or intolerances. His usual medication consisted of pantoprazole, rivaroxaban, cilostazol, thioctic acid, amlodipine, melatonin, ezetimibe, fenofibrate, tamsulosin, and insulin detemir.

He was admitted to our hospital for severe coronavirus pneumonia (COVID-19) requiring management in the intensive care unit without the need for mechanical ventilation. Subsequently, he developed prolonged febrile syndrome with no isolated germs in the microbiological studies. This condition was interpreted as inhospital pneumonia, so he was given treatment with vancomycin and meropenem for 7 days. The febrile syndrome persisted after the end of the antibiotic regimen. Having ruled out other causes of hyperthermia, on the 41st day after admission a transesophageal echocardiogram was performed, which showed the presence of a 3-mm vegetation on the aortic valve. Given the diagnosis of infective endocarditis of the native aortic valve with no isolated germs, empirical treatment was started with cefepime 2 g/8 h and vancomycin 1 g/12 h. Due to the need for prolonged intravenous antibiotic treatment with empirical coverage for MRSA in a patient with chronic kidney disease, we decided to replace vancomycin with daptomycin 10 mg/kg/24 h (dose = 900 mg/24 h). On the sixth day after administration, the patient presented with myoclonus at rest in the upper limbs. In view of this picture, metabolic causes were ruled out through laboratory studies (Table 1). Likewise, an analysis of concomitant drugs was performed in the search for another drug that could explain the phenomenon under study, with negative results (Table 2). In view of the suspicion of daptomycin-associated neurotoxicity, this antibiotic was changed back to vancomycin, with remission of the tremor. The patient evolved with progressive deterioration of kidney function and pharmacodermia in the upper and lower limbs and dorsum in the setting of supratherapeutic plasma levels of vancomycin (26.3 µg/mL). For this reason, vancomycin was once again discontinued and after 5 days, we decided to restart daptomycin at 8 mg/kg/24 h (dose = 720 mg/24 h). After the first infusion, the patient again presented with myoclonus in the upper and lower limbs, which later became generalized. On physical examination he was awake and oriented in the three spheres. His osteotendinous reflexes, cranial nerves, and

KEYWORDS
Daptomycin; Neurotoxicity syndromes; Myoclonus; Drug-related side effects and adverse reactions; Case reports.

PALABRAS CLAVE
Daptomicina; Neurotoxicidad; Mioclonías; Reacción adversa a medicamentos; Caso clínico.

strength were preserved. Involuntary movements persisted at night, making sleep difficult. Serial electroencephalograms were performed and showed no significant alterations, and so the movements were interpreted as asterixis secondary to daptomycin. Daptomycin was discontinued, with gradual improvement in the picture during the following week. During the periods in which the patient received daptomycin, CPK values were monitored, which always remained within the normal range. After this, the patient completed 4 weeks of intravenous antibiotic treatment with linezolid and cefepime. Given the patient's fragility and preferences, we decided not to replace the pacemaker and to continue with chronic suppressive antibiotic therapy with ciprofloxacin 500 mg/12 h plus oral minocycline 100 mg/12 h. We conducted a causality analysis using the algorithm developed by Naranjo *et al.*[4], which yielded a value of 8 for the reaction to daptomycin and 7 for the reaction to vancomycin. These values correspond to probable causality between exposure to and the respective reactions observed for each drug. Both adverse effects were reported to the National Pharmacovigilance System.

Prior to the completion of this manuscript, written informed consent was requested from the patient.

Table 1. Laboratory studies performed after possible daptomycin-associated myoclonus

Parameter (units), Normal values	Result
Hematocrit (%), 40-50	27
Hemoglobin (g/dL), 13-17	8.6
Leukocyte count (/µL), 4,000-10,000	8,300
Platelet count (/µL), 150,000-410,000	259,000
Natremia (mEq/L), 136-145	134
Kalemia (mEq/L), 3.6-5.1	3.6
Uremia (mg/dL), 18-55	45
Creatinemia (mg/dL), 0.73-1.18	1.19
Albuminemia (g/dL), 3.2-4.6	2.7
Calcemia (mg/dL), 8.8-10.0	8.5
Calcemia corrected for albuminemia (mg/dL)	9.5
Magnesemia (mg/dL), 1.6-2.6	1.6
Aspartate aminotransferase (IU/L), 5-34	14
Alanine aminotransferase (IU/L), < 50	11
Alkaline phosphatase (IU/L), 50-150	73
Total bilirubin (mg/dL), 0.5-1.2	0.6
Glycemia (mg/dL), 55-100	112
Plasma ammonia (µg/dL), 31-123	36
Creatine phosphokinase (IU/L), 30-200	9
Thyrotrophin (mIU/L) 0.35-4.93	0.53
Free T_4 (pmol/L) 9.0-19.0	12.1
Vitamin B_{12} (ng/mL) > 30	> 2,000

Discussion

Daptomycin is an effective antibiotic for infections caused by gram-positive organisms and is generally well tolerated, even in patients with comorbidity and under prolonged treatment[2,5]. Its most frequent adverse effect is myotoxicity, characterized by elevated CPK values, which in some cases results in myalgia and rhabdomyolysis, requiring discontinuation of the drug[5,6]. Other less frequently reported adverse reactions include digestive intolerance, allergic reactions, eosinophilia, and eosinophilic pneumonia[5,7]. Although there have been cases of kidney failure associated with daptomycin[5,7], its safety has been highlighted in patients with varying degrees of pre-existing nephropathy[8].

A literature search in Medline (keywords: daptomycin, neurotoxicity, myoclonus, adverse reactions) found that the data on daptomycin neurotoxicity comprised a case of paralysis of the external popliteal sciatic nerve[9] and a patient with posterior reversible encephalopathy syndrome[10]. As it was observed in our case, these adverse effects occurred with CPK values within the normal range. However, the World Health Organization database of adverse drug events (VigiAccess; available at: http://www.vigiaccess.org/) contains 574 registered cases of adverse effects at the level of the nervous system. Among these adverse events, at the level of the central nervous system, we highlight dizziness (8.4%), headache (8.2%), seizures (8.0%), and altered states of consciousness (8.7%).

We do not know the pathophysiological mechanism that may underlie the tremor. At onset, we ruled out possible metabolic causes that could explain it, such as hepatic encephalopathy, uremia, hypocalcemia, hypoglycemia, hyponatremia, hypomagnesemia, hyperthyroidism, and vitamin

Table 2. Description of the profile of pharmacological interactions extracted from the patient's medical prescription according to two online platforms (Lexicomp® and Medscape®). Note that none of the interactions detected would explain the observed myoclonus. Drugs assessed: daptomycin, cefepime, pantoprazole, rivaroxaban, cilostazol, thioctic acid, amlodipine, melatonin, ezetimibe, fenofibrate, tamsulosin, and insulin detemir

Detected interaction	Lexicomp® recommendation	Medscape® recommendation	Description
Amlodipine-melatonin	Monitor therapy	Not found	Decreased antihypertensive effect of amlodipine
Amlodipine-tamsulosin	Monitor therapy	Not found	Increased hypotensive effects of both drugs
Ezetimibe-fenofibrate	Monitor therapy	Minor. Significance unknown	Increased toxicity and in ezetimibe serum levels
Fenofibrate-insulin detemir	Not found	Monitor therapy	Increased effects of insulin
Melatonin-rivaroxaban	Not found	Monitor therapy	Increased anticoagulant effect of rivaroxaban
Melatonin-cilostazol	Not found	Monitor therapy	Increased antiplatelet effect of cilostazol
Pantoprazole-cilostazol	Not found	Monitor therapy	Increased toxicity of cilostazol
Rivaroxaban-cilostazol	Monitor therapy	Monitor therapy	Potentiation of the anticoagulant effect of rivaroxaban

B_{12} deficiency. Likewise, the patient had not received other drugs that could cause this manifestation. The reproduction of the clinical picture upon reintroduction of the drug strengthened our suspicion.

Although the pre-existing nephropathy of our patient could have been a predisposing factor for what was observed in the present case, the findings of Azanza and Quetglas[8] would suggest that there was a low probability of this having occurred.

Although we have not found any publications on daptomycin-associated myoclonus, we believe that our patient may not be the first to present with it. To date, there are 162 reports in VigiAccess associated with abnormal movements. This fact highlights the relevance and need to exercise pharmacovigilance to promote safety in health care and to encourage the construction of real-world safety profiles of the drugs used worldwide.

Funding

No funding.

Conflict of interest

No conflict of interests.

Bibliography

1. Durand GA, Raoult D, Dubourg G. Antibiotic discovery: history, methods and perspectives. Int J Antimicrob Agents. 2019;53(4):371-82. DOI: 10.1016/j.ijantimicag.2018.11.010
2. Kanafani Z, Boucher H, Fowler V, Cabell C, Hoen B, Miró J, *et al.* Daptomycin compared to standard therapy for the treatment of native valve endocarditis. Enferm Infecc Microbiol Clin. 2010;28(8):498-503. DOI: 10.1016/j.eimc.2009.07.015
3. Arbeit RD, Maki D, Tally FP, Campanaro E, Eisenstein BI, Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis. 2004;38(12):1673-81. DOI: 10.1086/420818
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al.* A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-45. DOI: 10.1038/clpt.1981.154
5. Durante-Mangoni E, Andini R, Parrella A, Mattucci I, Cavezza G, Senese A, *et al.* Safety of treatment with high-dose daptomycin in 102 patients with infective endocarditis. Int J Antimicrob Agents. 2016;48(1):61-8. DOI: 10.1016/j.ijantimicag.2016.04.022
6. Seaton RA, Menichetti F, Dalekos G, Beiras-Fernández A, Nacinovich F, Pathan R, *et al.* Evaluation of Effectiveness and Safety of High-Dose Daptomycin: Results from Patients Included in the European Cubicin® Outcomes Registry and Experience. Adv Ther. 2015;32(12):1192-205. DOI: 10.1007/s12325-015-0267-4
7. Higashi Y, Nakamura S, Tsuji Y, Ogami C, Matsumoto K, Kawago K, *et al.* Daptomycin-induced Eosinophilic Pneumonia and a Review of the Published Literature. Intern Med. 2018;15;57(2):253-8. DOI: 10.2169/internalmedicine.9010-17
8. Azanza J, Quetglas E. Seguridad de daptomicina en pacientes con insuficiencia renal. Med Clin (Barc). 2010;135(Supl3):S55-9. DOI: 10.1016/S0025-7753(10)70041-5
9. Villaverde Piñeiro L, Rabuñal Rey R, García Sabina A, Monte Secades R, García Pais MJ. Paralysis of the external popliteal sciatic nerve associated with daptomycin administration. J Clin Pharm Ther. 2018;43(4):578-80. DOI: 10.1111/jcpt.12666
10. Bitar De Zayas-Enríquez A, Soper C. Daptomycin-Induced Posterior Reversible Encephalopathy Syndrome (PRES). Case Rep Neurol Med. 2019;8756932:1-4. DOI: 10.1155/2019/8756932