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Case Report

Vancomycin infusion reaction: case report

Reação à infusão de vancomicina: relato de caso

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ABSTRACT: *Introduction:* The vancomycin infusion reaction, previously known as red man syndrome, is an adverse effect usually observed with the use of vancomycin in rapid intravenous infusion and that manifests itself, in most cases, minutes after administration of the first dose of the therapeutic scheme. However, there are rare situations in which this reaction manifests with slow intravenous infusion. In general, this regresses about 20 minutes after vancomycin is discontinued and treatment is instituted, nevertheless, more rarely, it can last from hours to days. *Objectives:* This study aims to inform, discuss and analyze the relevance of continuous monitoring and individualization of the dosage of this antibiotic, seeking to prevent the occurrence of adverse effects. *Method:* Case report of a patient who developed an infusion reaction to vancomycin two days after the end of the therapeutic regimen. *Results:* The patient reported showed partial regression of the adverse effect after nine days of the development of the condition and the institution of therapeutic measures. *Conclusion:* Thus, in addition to adjusting the dosage of this drug according to renal function, it is extremely important to be aware of the possibility of this adverse reaction occurring in unusual scenarios in medical practice.

Keywords: Vancomycin; Drug-related side effects and adverse reactions; Erythema; Drug hypersensitivity.

RESUMO: *Introdução:* A reação à infusão de vancomicina, anteriormente denominada de síndrome do homem vermelho, é um efeito adverso geralmente observado com o uso da vancomicina em infusão intravenosa rápida, e que se manifesta, na maior parte dos casos, minutos após a administração da primeira dose do esquema terapêutico. Entretanto, existem situações raras, em que essa reação também se manifesta na infusão intravenosa lenta. Em geral, essa reação regride cerca de 20 minutos após a suspensão da vancomicina e da instituição do tratamento, contudo, mais raramente, ela pode perdurar por horas a dias. *Objetivos:* Este estudo tem como objetivo informar, discutir e analisar a relevância do monitoramento contínuo e a individualização da dosagem desse antibiótico, buscando prevenir a ocorrência de efeitos adversos. *Método:* Relato de caso observado em uma paciente que desenvolveu reação à infusão de vancomicina dois dias após o término do esquema terapêutico. *Resultados*: A paciente relatada apresentou a regressão parcial do efeito adverso, após nove dias do desenvolvimento do quadro e da instituição das medidas terapêuticas. *Conclusão:* Além do ajuste da posologia desse fármaco de acordo com a função renal, é de suma importância estar atento à possibilidade de ocorrência dessa reação adversa em cenários não usuais na prática médica.

Palavras-chave: Vancomicina; Efeitos colaterais e reações adversas relacionados a medicamentos; Eritema; Hipersensibilidade a drogas.

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INTRODUCTION

Vancomycin is a tricyclic glycopeptide bactericidal antibiotic that has activity against Gram-positive bacteria[1]. Despite its nephrotoxicity[2] and potentially serious adverse effects, this antimicrobial is widely used in the hospital environment[3,4], especially in treatment of infections caused by multidrug-resistant microorganisms, in treatment of patients undergoing prolonged hospitalization and/or hospitalized in intensive care units (ICU), and in the care of people allergic to penicillin and cephalosporins[1,5].

Among its adverse effects, the vancomycin infusion-related reaction stands out[6]. Formerly called red man syndrome[7], this reaction usually results from the use of antibiotics in rapid venous infusion, that is, at a rate equal to or greater than 1 gram (g) per hour or 10 milligrams (mg) per minute[3,8]. In general, it starts in the first four to 10 minutes after the administration of the initial dose of the drug[8] and disappears about 20 minutes after the drug is discontinued[3].

The onset of a vancomycin infusion reaction in slow venous infusion may occur rarely, days after its administration[3]. In such cases, there may be a delay in the recognition of the condition and, consequently, a delay in the suspension of the medication and in the institution of support measures, which poses a threat to the patient's life[8].

OBJECTIVE

The aim of this study is to inform, discuss and analyze the relevance of continuous monitoring and individualization of the dosage of this antibiotic, seeking to prevent the occurrence of adverse effects.

METHOD

The case of a 68-year-old female patient admitted to the medical clinic ward is presented. She developed an infusion-related reaction to vancomycin two days after the end of medication, which had been previously administered for 21 days in slow venous infusion.

CASE REPORT

Patient I.S.A, female, 68 years old, white, born in Volta Redonda (RJ), was hospitalized in the medical clinic ward because of acute otitis media that evolved with the development of mastoiditis and left ear abscess. She had systemic arterial hypertension and Parkinson's dementia with significant dependence for performing basic activities of daily living (Katz Scale: <2) and for self-care (Palliative Performance Scale: 40).

Before hospital admission, she was on continuous use of bisoprolol 5 mg, Hidrion® (furosemide 40 mg + potassium chloride 100 mg), biperiden 2 mg, memantine 5 mg, Prolopa® (levodopa 200 mg + benserazide hydrochloride 50 mg), clonazepam 0.5 mg and Amytril® (amitriptyline 25 mg). Seven days earlier, she had started treatment for cystitis with Clavulin® (amoxicillin 875 mg + potassium clavulanate 125 mg). She had no relevant family history. She denied previous surgeries and other interventions. She reported an allergy to silver sulfadiazine.

On physical examination, the patient was in regular general condition, with episodes of confusion and disorientation, Glasgow coma scale 11, dehydrated (+1/4), pale (+2/4), febrile (38.3° C) and eupneic in room air. The presence of purulent drainage in the left ear was observed. Laboratory tests showed no changes and renal function was normal (serum creatinine: 0.7 mg/dl and serum urea: 28 mg/dl). Computed tomography of the mastoid showed the presence of infiltrate and fluid-filled air cells in the left mastoid process.

Initially, amoxicillin 1 g + potassium clavulanate 0.2 g, 1 sachet diluted in 100 ml of 0.9% saline was administered intravenously, every 8 hours, for a day. However, due to the patient's clinical characteristics and previous use of Clavulin®, antibiotic therapy with ceftriaxone 2 g, intravenous, 24/24 hours was started and maintained for 12 days. Four days after starting ceftriaxone, after confirmation of mastoiditis by computed tomography, it was associated with vancomycin 1 g, intravenously, every 8 hours, at a rate lower than 10 mg/min, administered for 21 days, without intercurrences. Seven days after the start of vancomycin, meropenem 1 g was introduced intravenously, every 8 hours and maintained for 10 days.

Two days after the end of vancomycin antibiotic therapy, the patient presented a sudden-onset erythematous and pruritic rash on the neck, upper trunk, back, hands and feet, indicative of the occurrence of a vancomycin infusion reaction. In addition, given the nephrotoxic effects of this antimicrobial, this reaction was accompanied by a significant worsening of renal function manifested by anuria and uremia (serum creatinine: 7.8 mg/dl and serum urea: 280 mg/dl), with the need for hemodialysis.

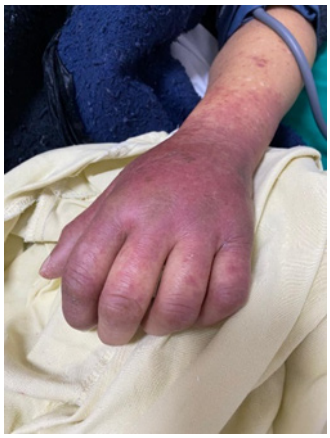

Figure 1: Vancomycin infusion reaction: left hand.

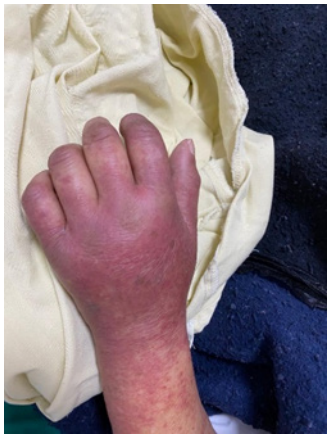

Figure 2: Vancomycin infusion reaction: left hand and wrist.

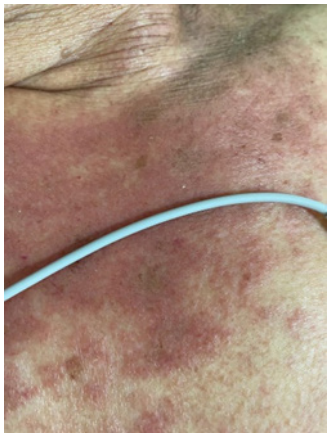

Figure 3: Vancomycin infusion reaction: cervical region.

Other possible differential diagnoses for this condition were: IgE-mediated anaphylactic reaction, angioedema, urticaria, DRESS syndrome (drug rash with eosinophilia and systemic symptoms) and Steven-Johnson syndrome. These diagnoses were ruled out by the clinical features of the erythema, indicative of a vancomycin infusion reaction.

Upon finding the vancomycin infusion reaction, treatment with promethazine 25 mg (1 tablet, via nasoenteral tube, 12/12 hours) and prednisone 20 mg (2 tablets, via nasoenteral tube, 24/24 hours) was started and maintained until partial disappearance of the reaction. The complete regression of the erythema occurred only in the upper region of the trunk and on the back, nine days after the onset of the condition, with a slight scaling of the skin in the previously affected area. As renal function was not recovered, the patient remained on hemodialysis.

DISCUSSION

Vancomycin infusion reaction, formerly called red man syndrome[7], is a non-IgE-mediated anaphylactoid reaction characterized by the sudden onset of an erythematous and pruritic rash on the face, neck, back and, less frequently, the extremities. In some cases, it is accompanied by possible life-threatening signs and symptoms, such as nausea and vomiting, hypotension, tachycardia, weakness, angioedema, muscle spasms, dyspnea and chest and/or back pain[3,8].

Figure 4: Regression of vancomycin infusion reaction with mild desquamation of the affected region.

This adverse effect usually results from the rapid intravenous infusion of vancomycin at a rate equal to or greater than 1 g/hour or 10 mg/minute[8]. In such conditions, it occurs in up to 47% of patients treated with this form of administration[4] within the first four to 10 minutes after application of the first dose of the therapeutic regimen[8]. However, in rare situations, the vancomycin infusion reaction is manifested even with the slow intravenous infusion of the antimicrobial and even days after its administration[8].

Diagnosis of this condition is clinical and treatment is performed with immediate interruption of drug use and administration of antihistamines[8]. In general, a good therapeutic response is observed, with erythema disappearing after 20 minutes, although in less frequent cases, this reaction can last for hours to days[1,3].

Although most cases do not show signs of severity and present a satisfactory therapeutic response, the occurrence of this reaction in unusual scenarios in medical practice can determine a delay in diagnosis and consequently, in the institution of treatment, which poses a threat to the patient's life[8]. As this adverse effect may occur in the following days, it is extremely important to monitor the patient, even after stopping the antimicrobial regimen[4], and to institute preventive measures[1,3].

One of the main ways of preventing this condition is to adjust the pharmacological dose according to the patient's renal function, since vancomycin is a drug mostly eliminated by glomerular filtration[1], and perform administration at a rate of less than 1 g/hour or 10 mg/minute[3,9]. In addition, serum levels of vancomycin, called

vancokinemia, can also be measured, and must be kept between 15 and 20 g/L[10]. However, vancokinemia is a very specific test available only in large centers, which constitutes a limitation to the monitoring of patients admitted to smaller hospitals.

CONCLUSION

Although the reaction to vancomycin infusion usually occurs in situations where rapid intravenous administration of this drug is performed and in the first minutes after the initial dose of the therapeutic regimen, it can also develop in cases where the correct antimicrobial dose is administered in slow infusion and even days after drug discontinuation.

In view of what has been exposed, it is extremely important to correctly follow the guidelines regarding drug administration by taking into account its dosage, dilution and infusion rate. It is necessary to be aware of the possibility of this adverse reaction occurring in unusual scenarios in medical practice, so that it can be promptly recognized and therapeutic measures instituted immediately, avoiding possible threats to the patient's life. The importance of this case report lies in the rarity of the vancomycin infusion reaction, which can contribute to epidemiological data of this condition.

Authors' participation: *Auriston Ferraz da Costa*: Orientation of the work and final approval for publication; *Maria Paula dos Reis Damasceno, Iasmim Garcia Júlio* and *Júlia Buzzato Rainer*: Conception and writing of the text, review of grammar and references.

REFERENCES

1. Gupta A, Biyani M, Khaira A. Vancomycin nephrotoxicity: myths and facts. Neth J Med. 2011;69(9):379-83. Available from: https://www.njmonline.nl/getpdf.php?id=1096

2. Pritchard L, Baker C, Leggett J, Sehdev P, Brown A, Bayley KB. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. Am J Med. 2010;123(12):1143-9. doi: https://doi.org/10.1016/j.amjmed.2010.07.025

3. Bruniera FR, Ferreira FM, Saviolli LR, Bacci MR, Feder D, da Luz Gonçalves Pedreira M, Sorgini Peterlini MA, Azzalis LA, Campos Junqueira VB, Fonseca FL. The use of vancomycin with its therapeutic and adverse effects: a review. Eur Rev Med Pharmacol Sci. 2015;19(4):694-700. Available from: https://www.europeanreview.org/article/8585

4. De Luca JF, Holmes NE, Trubiano JA. Adverse reactions to vancomycin and cross-reactivity with other antibiotics. Curr Opin Allergy Clin Immunol. 2020;20(4):352-61. doi: https://doi.org/10.1097/ACI.0000000000000665

5. Hicks RW, Hernandez J. Perioperative pharmacology: a focus on vancomycin. AORN J. 2011;93(5):593-6; quiz 597-9. doi: https://doi.org/10.1016/j.aorn.2010.09.031

6. Peng Y, Li CY, Yang ZL, Shi W. Adverse reactions of vancomycin in humans: a protocol for meta-analysis. Medicine (Baltimore). 2020;99(38):e22376. doi: https://doi.org/10.1097/MD.0000000000022376

7. Alvarez-Arango S, Ogunwole SM, Sequist TD, Burk CM, Blumenthal KG. Vancomycin infusion reaction - moving beyond "Red Man Syndrome". N Engl J Med. 2021;384(14):1283-6. doi: https://doi.org/10.1056/NEJMp2031891

8. Martel TJ, Jamil RT, King KC. Vancomycin Flushing Syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK482506/

9. Irani AM, Akl EG. Management and prevention of anaphylaxis. F1000Res. 2015;4:F1000 Faculty Rev-1492. doi: https://doi.org/10.12688/f1000research.7181.1

10. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, Mueller BA, Pai MP, Wong-Beringer A, Rotschafer JC, Rodvold KA, Maples HD, Lomaestro BM. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020;77(11):835-64. doi: https://doi.org/10.1093/ajhp/zxaa036.

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