

Vancomycin Induced Neutropenia: A Case Report

Jennifer A Crozier^{1*}, Abhisek Swaika¹, Nancy Vendrell² and Laura Finn¹

¹Department of Hematology and Oncology, Mayo Clinic, Jacksonville, Florida, USA

²Department of Pharmacy, Mayo Clinic, Jacksonville, Florida, USA

Abstract

Vancomycin is a glycopeptide antibiotic with widespread use since 1958. Vancomycin is clinically indicated for the treatment of methicillin-resistant strains of coagulase negative and coagulase positive staphylococcal infections, gram-positive penicillin-resistant infections and as an alternative treatment for penicillin-allergic patients. Vancomycin induced neutropenia is a rare side effect. We present the case of a 23 year old man with recurrent fevers and persistently positive blood cultures growing viridans group streptococci. He was found to have endocarditis requiring aortic valve replacement. Due to the patient's allergies he was treated with IV vancomycin therapy. This resulted in the uncommon adverse event of vancomycin induced neutropenia. The patient subsequently responded to granulocyte colony stimulating factor. Vancomycin induced neutropenia is an uncommon but serious adverse reaction with the potential for morbidity and mortality. Further guidelines are needed for leukocyte monitoring during vancomycin therapy and the use of granulocyte colony stimulating factor to treat this adverse effect.

Keywords: Adverse effects; Vancomycin; Antibiotics; Neutropenia; Hematologic toxicity

Introduction

Vancomycin is a glycopeptide antibiotic with widespread use since 1958 [1]. Early preparations were dubbed "Mississippi mud" because of the brown color and marked impurity and toxicity which has improved since the 1990s [2]. Vancomycin exhibits concentration independent bactericidal activity by the inhibition of bacterial cell wall synthesis [3]. It also exhibits minimal concentration dependent activity [4]. In patients with normal renal function, vancomycin has a half-life of 4-8 hours with 80-90% elimination by the kidney within 24 hours [1]. Vancomycin is clinically indicated for methicillin-resistant strains of coagulase negative and coagulase positive staphylococcal infections, including bacteremia, endocarditis, pneumonia, cellulitis and osteomyelitis [1]. Vancomycin remains a major therapeutic option for bacterial endocarditis in penicillin-allergic patients and those patients with gram-positive penicillin-resistant infections. Adverse events for vancomycin include anaphylaxis, abdominal pain, ototoxicity and nephrotoxicity. Vancomycin induced neutropenia is an adverse side effect that is rarely reported.

Case Summary

A 23 year-old man presented to the emergency department with a 12 week history of recurrent intermittent fevers to 39.0 degrees Celsius. The patient was admitted to the internal medicine service for further evaluation and treatment. He had no known significant medical problems and no surgical history. His social history was remarkable for a college student, living at home with his parents and no previous sexual activity. He drank 1-2 alcoholic beverages weekly; he denied any current or previous tobacco or illicit drug use. He took no medications regularly but had recently been using acetaminophen for his fevers. The patient had a history of angioedema with exposure to penicillins and cephalosporins. Family history was noncontributory. Patient had dental surgery approximately 16 weeks prior to the hospital presentation and he did not require any prophylactic antibiotics. His physical examination was remarkable for a height of 174 cm, weight of 75.8 kg, fever of 38.2 degrees Celsius, an IV/VI systolic ejection murmur loudest at the left upper sternal border with radiation to the carotid arteries and an Osler's node on his right thumb. At this point the differential diagnosis included a viral infection, bacterial infection or malignancy. His basic laboratory data revealed a white blood cell count (WBC) of 6.9×10^3 cells/mm³ (Normal: $3.5-10.5 \times 10^3$ cells/mm³), normal

absolute neutrophil count (ANC) of 5.9×10^3 cells/mm³ (Normal: $1.7-7.0 \times 10^3$ cells/mm³), hemoglobin 10.0 (Normal: 13.5-17.5 g/dl) and creatinine 0.7 (Normal: 0.8-1.3 mg/dl). The patient had a normocytic anemia. Hemolysis evaluation with a peripheral smear, bilirubin, and haptoglobin was negative. Two peripheral venous blood cultures were drawn from separate left and right peripheral venous sites. The initial blood cultures were both positive for viridans group streptococci. Repeat blood cultures were obtained and were persistently remarkable for viridans streptococci. The patient had no history of bacteremia. The infectious disease team was consulted for antibiotic management and the allergy team was consulted due to the patient's history of angioedema with exposure to penicillins and cephalosporins. The patient and both the allergy and infectious disease team felt most comfortable avoiding penicillins and cephalosporins. Vancomycin therapy was initiated at a rate of 20 mg/kg=1500 mg IV q12 hours. A trough level was appropriate at 9.5 ug/ml. In evaluating the etiology of the bacteremia there was concern for endocarditis and a transesophageal echocardiogram was performed revealing a bicuspid aortic valve (a congenital abnormality not known to the patient) with an aortic root periannular abscess and severe aortic valve regurgitation. With the patient's positive blood cultures and abnormal echocardiogram fulfilled the two major criteria needed for clinical evidence of infective endocarditis. Due to these severe abnormalities cardiothoracic surgery was consulted and subsequently performed an aortic root replacement with a homograft. As the patient recovered from surgery his repeat blood cultures were negative. He was discharged home to complete a 6 week course of IV vancomycin, his other medications at discharge included metoprolol and oxycodone.

The patient did well at home for 8 days until he was found by his home healthcare nurse to be febrile and his CBC revealed a low total

***Corresponding author:** Jennifer A Crozier, Department of Hematology and Oncology, Mayo Clinic, 4500 San Pablo Road, Jacksonville, Florida 32224, USA, Tel: 904-953-7290; E-mail: Crozier.Jennifer@mayo.edu

Received December 10, 2014; **Accepted** January 24, 2015; **Published** January 24, 2015

Citation: Crozier JA, Swaika A, Vendrell N, Finn L (2015) Vancomycin Induced Neutropenia: A Case Report. J Clin Case Rep 5: 478. doi:10.4172/2165-7920.1000478

Copyright: © 2015 Crozier JA, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

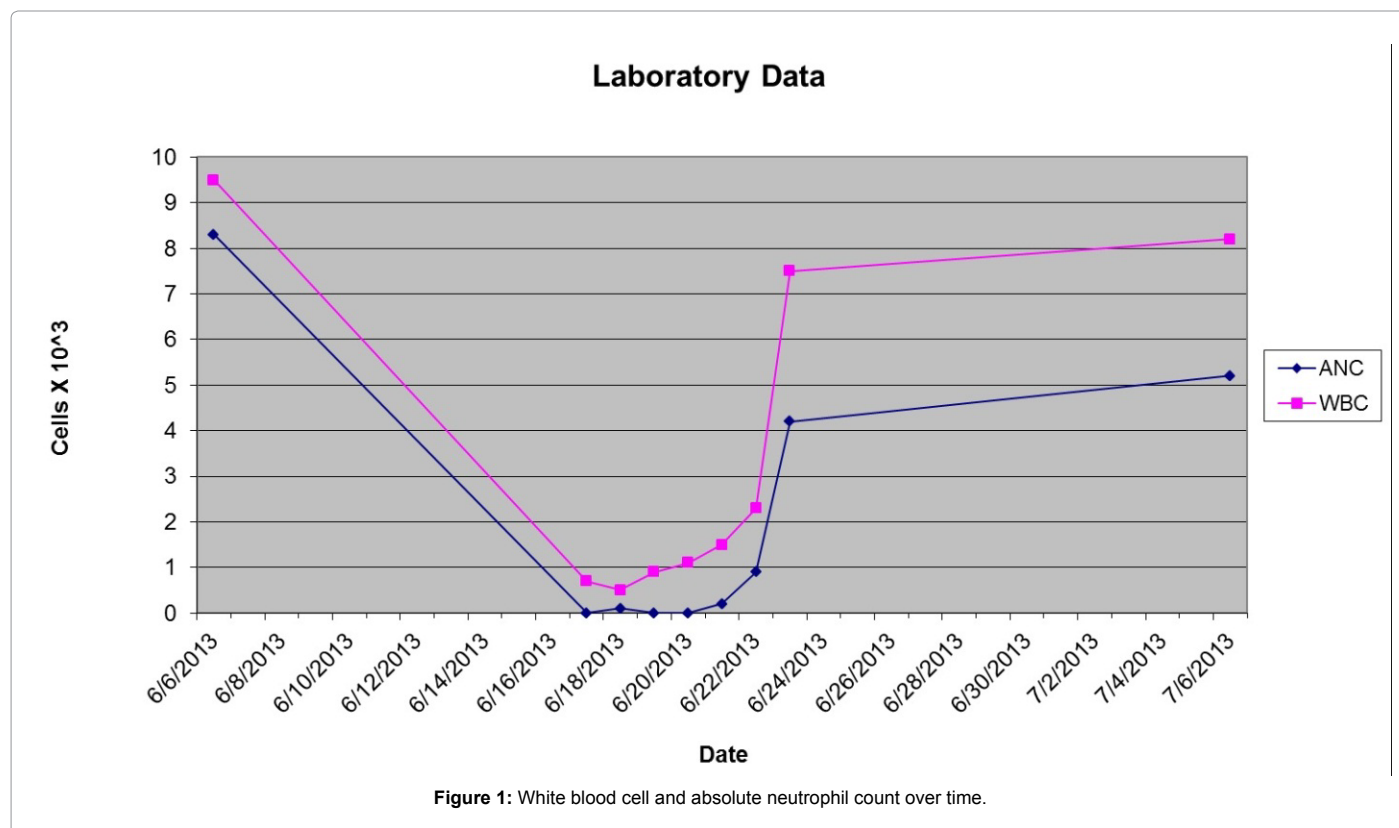


Figure 1: White blood cell and absolute neutrophil count over time.

white blood cell count of 0.7×10^3 cells/mm³ and neutropenia with an ANC of 0.0×10^3 cells/mm³, lymphopenia (ALC of 0.4×10^3 cells/mm³), and low eosinophil count of 0.03×10^3 cells/mm³. He was re-admitted to the internal medicine service where he had no complaints other than diaphoresis during the fevers. On examination he was found to be febrile at 38.3 degrees Celsius and also had a diffuse, erythematous, blanchable macular rash on his torso. Blood cultures, urinalysis with culture and stool cultures were all negative. A chest x-ray was unremarkable. A transthoracic echocardiogram only revealed the aortic valve prosthesis. The differential diagnosis included persistent or superimposed infection, malignancy and drug reaction. Vancomycin therapy was discontinued and meropenem was initiated. The patient's fevers resolved after vancomycin therapy was discontinued. His rash was evaluated by dermatology and the rash was consistent with a mild morbilliform drug eruption and resolved during the hospitalization. No other etiologies of the neutropenia could be found with clearing of the bacteremia and no other confounding medications found. According to the Naranjo probability scale the neutropenia is likelihood of neutropenia due to Vancomycin is probable [5]. The patient was evaluated by the hematology team and started on Granulocyte Colony Stimulating Factor (GCSF) therapy for 5 days. His neutropenia subsequently resolved after 5 days with the ANC improving to 4.2×10^3 cells/mm³ and he was discharged home to complete a course of ertapenem IV every 24 hours. His CBC was followed after discharge and remained within normal limits (Figure 1).

Discussion

Vancomycin induced neutropenia is an uncommon but serious adverse reaction with the potential for morbidity and mortality due to the risk of infection. In 2006, a retrospective chart review at the University of New Mexico of 114 patients treated with home IV therapy

showed fourteen (12%) cases of vancomycin-induced neutropenia; 4 cases (3.5%) had neutrophil counts below 500 cells/ μ L [6]. Other retrospective analyses in hospitalized patients including general medical and cardiothoracic surgery patients show an estimated incidence of 2-8% [7,8].

No association has been found in regards to trough concentrations, dosage or total cumulative dosing [9]. The onset of neutropenia does appear to occur with prolonged use with a minimum of 7 days and mostly occurring at least 20 days after therapy initiation [9]. The mechanism of action of the neutropenia is controversial. Multiple theories have been postulated including an immunological mechanism with an IgG or IgM immune-mediated hypersensitivity reaction [10]. Evidence to support this hypothesis includes studies revealing bone marrow samples with granulocyte-specific antibodies [11,12]. Another proposed mechanism is direct toxicity to the bone marrow [13]. This has been supported by hypocellular marrow with maturation arrest on bone marrow biopsy [13].

Current American Society of Health-System Pharmacists and the Infectious Diseases Society of America (ASHP/IDSA) guidelines do not discuss the need of regular monitoring of leukocyte count while receiving vancomycin [14]. The medication prescribing information does recommend periodic monitoring of leukocyte count but does not define intervals or guidelines for discontinuation [15]. Two case reports have shown successful treatment of vancomycin-induced neutropenia with GCSF where the continuation of vancomycin therapy was necessary [10]. No guidelines or recommendations exist for the use of GCSF in vancomycin-induced neutropenia [15]. Patients undergoing prolonged vancomycin therapy should remain under close clinical care with regular laboratory testing for blood counts at least once weekly.

Conclusion

Vancomycin is a commonly used antibiotic. Vancomycin-induced neutropenia is an uncommon adverse event associated with its use. The case presented here shows resolution of vancomycin-induced neutropenia with GCSF therapy. Guidelines are needed for monitoring of blood counts while on vancomycin therapy.

References

1. Nailor, Sobel (2009) Antibiotics for gram-positive bacterial infections: vancomycin, teicoplanin, quinupristin/dalfopristin, oxazolidinones, daptomycin, dalbavancin, and telavancin. *Infect Dis Clin North Am.* 23: 965-982.
2. Linda S Elting, Edward B Rubenstein, Danna Kurtin, Kenneth R, John Fangtang (1998) Mississippi mud in the 1990s: risks and outcomes of vancomycin-associated toxicity in general oncology practice. *Cancer* 83: 2597-2607.
3. Deborah LH, Ray C, Dmitri VD, Joey L, Terry W et al. (2005) Telavancin, a multifunctional lipoglycopeptide, disrupts both cell wall synthesis and cell membrane integrity in methicillin-resistant *Staphylococcus aureus*. *Antimicrob Agents Chemother.* 49: 1127-1134.
4. Cunha BA, Quintiliani R, Deglin JM, IZard MW, Nightingale CH (1981) Pharmacokinetics of vancomycin in anuria. *Rev Infect Dis.* S269-S272.
5. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, et al. (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30: 239-245.
6. Pai MP, Mercier RC, Koster SA (2006) Epidemiology of vancomycin-induced neutropenia in patients receiving home intravenous infusion therapy. *Ann Pharmacother* 40: 224-228.
7. Farber B F, Moellering R C (1983) Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. *Antimicrob Agents Chemother* 23: 138-41.
8. Morris A, Ward C (1991) High incidence of vancomycin-associated leucopenia and neutropenia in a cardiothoracic surgical unit. *J Infect* 22: 217-223.
9. Black E, Lau TT, Ensom MH (2011) Vancomycin-induced neutropenia: is it dose- or duration-related. *Ann Pharmacother* 45: 629-638.
10. Lai KK, Kleinjan J, Belliveau P (1996) Vancomycin-induced neutropenia treated with granulocyte colony-stimulating factor during home intravenous infusion therapy. *Clin Infect Dis.* 23: 844-845.
11. Domen RE, Horowitz S (1990) Vancomycin-induced neutropenia associated with anti-granulocyte antibodies. *Immunohematology* 6: 41-43.
12. Schwartz (2002) Vancomycin-induced neutropenia in a patient positive for an antineutrophil antibody. *Pharmacotherapy* 22: 783-788.
13. Olaison L, Belin L, Hogevik H, Alestig K (1999) Incidence of beta-lactam-induced delayed hypersensitivity and neutropenia during treatment of infective endocarditis. *Arch Intern Med* 159: 607-615.
14. Rybak M (2009) Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm* 66: 82-98.
15. http://www.pfizer.com/files/products/uspi_vancomycin_5g_bulk.pdf