

Glycopeptide-Induced Neutropenia: Cross-Reactivity Between Vancomycin and Teicoplanin

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Tenicoplanin is a glycopeptide antibiotic, similar to vancomycin in structure and activity. Both are effective against gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci. Teicoplanin is reported to be as effective as vancomycin but with fewer adverse effects.¹ However, doses of teicoplanin used in studies are now considered insufficient; therefore, studies of the therapeutic regimens used in clinical practice are needed to evaluate the toxicity of teicoplanin.

Previously, red man syndrome was the most common toxicity of vancomycin. Red man syndrome is an anaphylactic reaction that typically presents as pruritus and an erythematous rash involving the face, neck, and upper trunk, due to the degranulation of mast cells and basophils and resulting in the release of histamine independent of preformed immunoglobulin (Ig) E or complement. Other adverse reactions to vancomycin include fever, rash, phlebitis, nephrotoxicity, ototoxicity, thrombocytopenia, and neutropenia.² Adverse reactions most frequently associated with teicoplanin treatment are local hypersensitivity reactions, such as itching and drug fever. Cases of neutropenia related to teicoplanin treatment have been described.³

Neutropenia is commonly defined by conditions where in a patient's absolute neutrophil count (ANC) is less than $1.5 \times 10^3/\text{mm}^3$, and agranulocytosis is defined as ANC less than $0.5 \times 10^3/\text{mm}^3$. Neutropenia associated with van-

OBJECTIVE: To report teicoplanin-related neutropenia that developed after an episode of neutropenia induced by vancomycin therapy.

CASE SUMMARY: A 57-year-old female suffered from osteomyelitis of the left humerus, with a white blood cell (WBC) count of $2.8 \times 10^3/\text{mm}^3$ and absolute neutrophil count (ANC) of $0.28 \times 10^3/\text{mm}^3$, occurring after 24 days of vancomycin therapy. Vancomycin was changed to teicoplanin and the agranulocytosis resolved 4 days later. However, a new episode of neutropenia, with a WBC count of $2.8 \times 10^3/\text{mm}^3$ and ANC of $0.448 \times 10^3/\text{mm}^3$, occurred 11 days after teicoplanin initiation. Agranulocytosis resolved 4 days following withdrawal of teicoplanin.

DISCUSSION: Because of the close time relationship between drug administration and the development of symptoms and signs, as well as between drug withdrawal and changes in WBC count and ANC, the episodes of neutropenia were suspected to be drug related. Teicoplanin-induced agranulocytosis that followed vancomycin-induced agranulocytosis suggests a possible cross-reactivity between the 2 drugs. Both reactions were categorized as probable according to the Naranjo probability scale.

CONCLUSIONS: For all patients with vancomycin-induced neutropenia, possible cross-reactivity of teicoplanin should be monitored.

KEY WORDS: cross-reactivity, glycopeptide, neutropenia, teicoplanin, vancomycin.

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comycin therapy was reported to be 2%⁴ to 8%⁵ and mainly associated with prolonged therapy, although a recently published case-cohort study estimated that 12% of all vancomycin use results in neutropenia.⁶

According to previous reports, teicoplanin-induced neutropenia was observed to be 0.88% (3/342),⁷ 1.6% (1/64),⁸ and 11.1% (1/9).⁹ Thus, incidence of neutropenia associated with these 2 glycopeptides is diverse. As teicoplanin has been recommended for use in patients with adverse reactions to vancomycin, we discuss here a case of vancomycin-induced neutropenia with a recurrence induced by the subsequent teicoplanin therapy. To the best of our knowledge, as of March 2007, such a case has not been reported in the literature.

Author information provided at the end of the text.

Case Report

A 57-year-old female was admitted to the hospital on April 13, 2006, with discharge from a surgical incision site on the left humerus. The patient had undergone open reduction and internal fixation for humeral and clavicular fractures suffered in a traffic accident 15 days before presentation.

On the day of admission, discharge from the surgical wound on the patient's left arm was noted. In addition, some turbid, serous discharge from the left popliteal skin incision site was found during wound dressing. She had no past history of tuberculosis, HIV infection, diabetes mellitus, hyperlipidemia, hypertension, or any major organ disease. She had not been taking any medication and had not experienced allergies to drugs or food in the past.

Her vital signs on admission were blood pressure 125/71 mm Hg, pulse 116 beats/min, respiration rate 20 breaths/min, and tympanic temperature 37.2 °C. Physical examination showed postoperative incision wounds on both arms, the right upper chest wall, and a skin defect on the left popliteal fossa. The surgical wound on the left arm was oozing serosanguinous fluid, and there was purulent discharge from the left popliteal skin defect. Both granulation and necrosis were present. Wound infection was tentatively diagnosed.

On hospital day 1, blood and wound cultures were performed. Serum C-reactive protein (CRP) was 30.7 mg/dL and erythrocyte sedimentation rate (ESR) was 76 mm/h. The patient became febrile (39 °C) on hospital day 2. With a working diagnosis of humerus wound infection with gram-positive cocci bacteremia, intravenous vancomycin 1 g every 12 hours was initiated on hospital day 5. The concomitantly administered medications during the hospital

course are listed in Figure 1. Based on serum concentration monitoring designed to maintain vancomycin peak concentrations of 25–40 µg/mL and trough concentrations of 8–15 µg/mL, a dose of 750 mg every 8 hours was maintained from day 9 of hospitalization until the drug was discontinued.

Fever subsided after vancomycin treatment was initiated, and the final reports of both the blood and wound culture tests showed oxacillin-resistant *S. aureus*. After debridement of the surgical wound, the possibility of osteomyelitis was considered. The infectious diseases consultant recommended that vancomycin be maintained for 6 weeks.

The woman's complete blood cell count and biochemistry parameters were regularly monitored. Her renal and liver function remained within normal limits during the entire hospital course. However, leukopenia (WBC count $2.8 \times 10^3/\text{mm}^3$) with eosinophilia (9%) and neutropenia (ANC $0.28 \times 10^3/\text{mm}^3$) developed after 24 days of vancomycin therapy. Vancomycin-induced neutropenia was suspected and the drug was withdrawn. Three doses of intravenous teicoplanin 400 mg every 12 hours were administered; the dose was then changed to 400 mg once daily. By the fourth day of teicoplanin therapy, the WBC count returned to normal limits (WBC count $4.6 \times 10^3/\text{mm}^3$ and ANC $1.6 \times 10^3/\text{mm}^3$). The WBC count reached $5.6 \times 10^3/\text{mm}^3$ and ANC $3.6 \times 10^3/\text{mm}^3$ by the sixth day of teicoplanin therapy. Bone and gallium-67 scans performed on May 17, 2006, confirmed the diagnosis of osteomyelitis. It was decided to continue teicoplanin for 6 weeks.

Unfortunately, after 11 days of teicoplanin therapy, another episode of neutropenia occurred (WBC count $2.8 \times 10^3/\text{mm}^3$ and ANC $0.45 \times 10^3/\text{mm}^3$; WBC count $2.6 \times 10^3/\text{mm}^3$ and

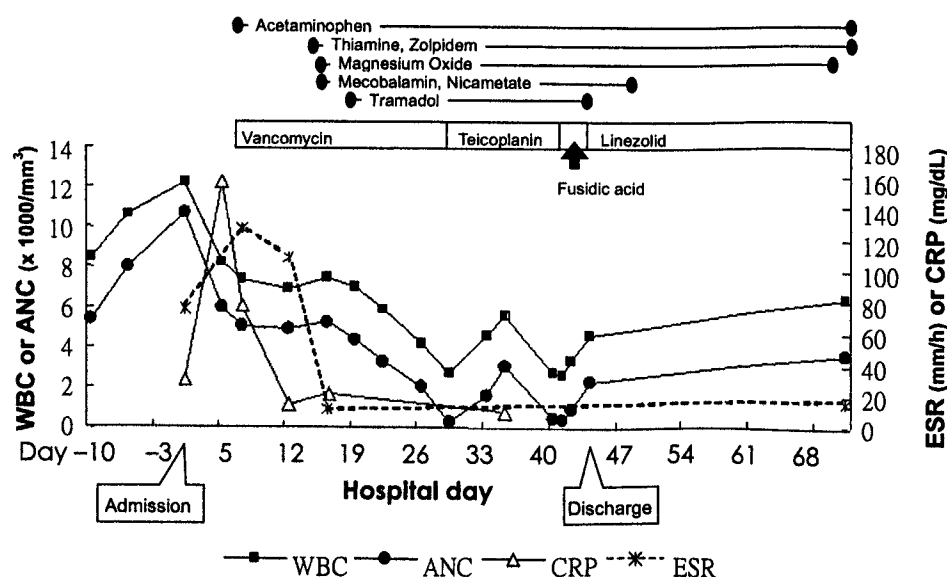


Figure 1. The relationship between administration and withdrawal of vancomycin and teicoplanin. ANC = absolute neutrophil count; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; WBC = white blood cell.

ANC $0.36 \times 10^3/\text{mm}^3$ were reported the next day). Drug-induced neutropenia was considered; teicoplanin was immediately stopped and fusidic acid 500 mg 3 times daily orally was begun. The patient's WBC count returned to within normal limits 4 days later (WBC count $4.6 \times 10^3/\text{mm}^3$ and ANC $2.33 \times 10^3/\text{mm}^3$). On hospital day 45, the patient was discharged, and linezolid 600 mg twice daily orally was administered for another 2 months. Follow-up 1 month after discharge revealed WBC count $6.4 \times 10^3/\text{mm}^3$ and ANC $3.64 \times 10^3/\text{mm}^3$.

The patient's other medications included acetaminophen, mecobalamin, thiamine, nicametate (a nicotinic acid derivative), zolpidem, and tramadol. These were not changed during the course of the 2 episodes of agranulocytosis. Although many etiologies are associated with neutropenia, the major causes leading to its acute onset are viral infections and adverse drug reactions. Since our patient did not have any underlying neutropenia-related chronic disease and rapid recovery of her WBC count occurred after withdrawal of teicoplanin, a bone marrow biopsy was not performed. No virus was isolated from her blood samples, while serologic studies were negative for cytomegalovirus IgM, Epstein-Barr viral capsid antigen IgM, and HIV antibody.

Reviewing the course of treatment (Figure 1), we strongly suspected the probability of the adverse effects of glycopeptides. Upon applying the Naranjo probability scale, we categorized neutropenia related to both vancomycin and teicoplanin in this patient as probable.¹⁰

Discussion

From the clinical observation and the changes in laboratory data of ESR and CRP,¹¹ the treatment for osteomyelitis was rather successful in this case. In the absence of any underlying chronic disease and no evidence of viral infection in the patient, both the clinical pharmacist and the infectious diseases consultant in charge of the case immediately suspected that these 2 episodes of agranulocytosis were adverse drug reactions. Because both vancomycin and teicoplanin were the only medications withdrawn on both episodes of agranulocytosis and immediate recovery was observed in both instances, the roles of these drugs in neutropenia were strongly suspected. Moreover, the results of all tests conducted to identify bacterial and viral infection were negative.

Vancomycin-induced neutropenia mainly occurs after at least 7 days of therapy and generally does not correlate well with serum drug concentrations or dosages.⁶ All case reports from the medical literature indicate that, once vancomycin is discontinued, the WBC count and ANC rapidly return to normal, generally within 2–5 days.^{6,12,13} In our patient, agranulocytosis developed after 24 days of van-

comycin therapy and recurred after 11 days of teicoplanin therapy. Each episode of neutropenia resolved by the fourth day following discontinuation of the antibiotic.

In this patient, the onset of drug-induced neutropenia was much quicker with teicoplanin than with vancomycin, suggesting a potential cross-reaction between these 2 glycopeptides. However, the evidence of cross-reactivity between teicoplanin and vancomycin remains inconclusive. In general practice, teicoplanin is still used as an alternative for vancomycin when vancomycin-related adverse effects occur. Sanche et al.¹⁴ reported a case of vancomycin-induced neutropenia resolving after substitution with teicoplanin. Cross-reactivity of β -lactam antibiotic-induced neutropenia has been reported and is well known in clinical practice, with structural similarity as the molecular basis.¹⁵

In contrast to successful substitution with teicoplanin, cases implying cross-reactivity between teicoplanin and vancomycin have also been reported.^{16–21} Most of these cases manifested as red man syndrome, skin lesions, and vasculitis. Quite different from the reported cases mentioned above, our case presents cross-reactivity in terms of hematologic abnormality, which has not been previously reported. The unusual presentation of sequential episodes of agranulocytosis by vancomycin and teicoplanin strongly suggests the possibility of cross-reactivity.

Conclusions

Teicoplanin may be used as an alternative for vancomycin in most conditions. Even though cross-reactivity between these drugs is rare, the sequential episodes of agranulocytosis in our patient suggest some potential cross-reactivity between the 2 agents. For all patients with severe vancomycin-induced adverse reactions, such as neutropenia, clinicians should be aware of the possible cross-reactivity with teicoplanin.

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EXTRACTO

OBJETIVO: Este es un reporte de un caso de neutropenia relacionada a teicoplanin que se desarrolló luego de un episodio de neutropenia inducida por vancomicina.

RESUMEN: Una mujer de 57 años padeció de osteomielitis del húmero izquierdo, con un conteo de células blancas de $2.8 \times 10^3/\text{mm}^3$ y un conteo absoluto de neutrófilos de $0.28 \times 10^3/\text{mm}^3$, luego de 24 días de una terapia con vancomicina. Se sustituyó la vancomicina por teicoplanin y la agranulocitosis resolvió 4 días más tarde. Sin embargo, un nuevo episodio de neutropenia con un conteo de células blancas de $2.8 \times 10^3/\text{mm}^3$ y un conteo absoluto de neutrófilos de $0.448 \times 10^3/\text{mm}^3$, ocurrió 11 días luego de haber comenzado la terapia con teicoplanin. Luego de discontinuar el uso de teicoplanin, la agranulocitosis resolvió 4 días más tarde.

DISCUSIÓN: Por la corta relación temporal entre la administración del medicamento y el desarrollo de los signos y síntomas, así como entre la discontinuación del medicamento y el cambio en los conteos de células blancas, se sospecha que los episodios de neutropenia sean relacionados al medicamento. La agranulocitosis inducida por teicoplanin luego de la agranulocitosis inducida por vancomicina sugiere una posible reactividad cruzada entre los dos medicamentos. Al utilizar el algoritmo de Naranjo para reacciones adversas a medicamentos, ambas reacciones pueden ser catalogadas como “probables”.

CONCLUSIONES: En todos los pacientes de neutropenia inducida por vancomicina se debe vigilar una posible reacción cruzada con teicoplanin.

Annette Pérez

RÉSUMÉ

OBJECTIF: Rapporter un cas de neutropénie induite par la teicoplanine qui s'est développé après un épisode de neutropénie induite par la vancomycine.

RÉSUMÉ DU CAS: Une femme de 57 ans souffrant d'une ostéomyélite de l'humérus gauche a développé un taux de globules blancs atteignant $2.8 \times 10^3/\text{mm}^3$ et un taux absolu de neutrophiles de $0.28 \times 10^3/\text{mm}^3$ après 24 jours de thérapie à la vancomycine. Cette dernière fut changée pour la teicoplanine et l'agranulocytose s'est résorbée 4 jours plus tard. Cependant, un nouvel épisode de neutropénie caractérisé par un taux de globules blancs atteignant $2.8 \times 10^3/\text{mm}^3$ et un taux absolu de neutrophiles de $0.448 \times 10^3/\text{mm}^3$ s'est développé 11 jours après le début de la teicoplanine. Suite à son retrait, l'agranulocytose s'est résorbée 4 jours plus tard.

DISCUSSION: Considérant la relation temporelle entre l'administration du médicament et le développement des signes et symptômes ainsi qu'entre le retrait du médicament et le changement dans les taux de globules blancs et de neutrophiles, les épisodes de neutropénie sont suspectés avoir été induits par les médicaments. L'agranulocytose qui fut induite par la teicoplanine et qui a suivi celle induite par la vancomycine suggère une possible réaction croisée entre ces médicaments. En appliquant l'algorithme de Naranjo, ces deux réactions sont catégorisées comme étant probables.

CONCLUSIONS: Pour les patients ayant subi une neutropénie induite par la vancomycine, une possible réaction croisée avec la teicoplanine devrait être monitorée.

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