Vancomycin-Induced Neutropenia: Is it Dose- or Duration-Related?

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OBJECTIVE: To systematically evaluate the literature to determine whether vancomycin-induced neutropenia is dose- or duration-related and provide clinicians with feasible treatment alternatives.

DATA SOURCES: A literature search of PubMed (1949-November 2010), MEDLINE (1950-November 2010), EMBASE (1980-November 2010), and *International Pharmaceutical Abstracts* (1970-November 2010) was performed using the terms vancomycin, neutropenia, and leukopenia. Citations from publications were reviewed for additional references.

STUDY SELECTION AND DATA EXTRACTION: Studies and case reports were included if they reported neutropenia with vancomycin administration and excluded if they did not describe vancomycin dosages and/or concentrations, or if neutropenia resolved while the patient was still receiving vancomycin. Cases with significant confounders and those in which authors provided minimal information about patients were also excluded.

DATA SYNTHESIS: Seven retrospective chart reviews (ie, case series) and 33 case reports were identified. Of these, 3 retrospective reviews and 26 case reports met inclusion criteria. To our knowledge, no prospective studies have assessed this clinical complication. Data suggest that vancomycin-induced neutropenia may not be completely related to daily dosages, total cumulative dosage, or supratherapeutic vancomycin concentrations. Furthermore, evidence suggests that neutropenia is more likely associated with therapy longer than 7 days, with the majority of episodes occurring beyond 20 days of therapy. Given these findings, a practical approach is to monitor white blood cell (WBC) count with a differential (including absolute neutrophil count) once a week in patients who are receiving vancomycin for more than 7 days.

CONCLUSIONS: Vancomycin-induced neutropenia is most likely associated with prolonged vancomycin exposure. Patients receiving vancomycin for longer than 7 days should have WBC count, differential, monitored weekly. Vancomycin should be discontinued if there is a high clinical suspicion of it causing neutropenia, and an alternative agent should be initiated. Prospective case-controlled studies are needed to better characterize this adverse event.

KEY WORDS: neutropenia, systematic review, vancomycin.

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Drug-induced neutropenia is a serious condition resulting in decreased absolute neutrophil count (ANC) and subsequent increased risk of infection. Andres et al. summarized the literature in 2002 and reported drug-induced neutropenia in a broad range of drug classes including antimicrobials, analgesics, antipsychotics and sedatives, anticonvulsants, antithyroid drugs, cardiovascular drugs, and antihistamines.[1] Mortality rates of non-chemotherapy drug-induced agranulocytosis were reported as high as 16% in a retrospective review.[2] Antibiotics have been implicated as a common non-chemotherapy drug-induced cause of neutropenia, with a mortality rate of 5%.[3,4]

Vancomycin-induced neutropenia, defined as an ANC less than 1000/μL, has been reported to occur at rates of 2-12%.[5-8] The first 2 case reports were published by Dangerfield and colleagues in 1960, shortly after the introduction of the drug.[5] Since these initial cases, vancomycin-induced neutropenia has continued to be reported in the literature. Earlier formulations of vancomycin had impurities that may have contributed to higher incidences of adverse effects, such as neutropenia.[9] Although the puri-

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ty of current formulations has improved significantly, the cause of neutropenia has yet to be determined and neutropenia continues to be observed in clinical practice.

Despite increasing awareness of vancomycin-induced neutropenia, few reviews have been published summarizing the characteristics of this reaction.[10] To our knowledge, no systematic review has been published to address the question of whether vancomycin-induced neutropenia is dose- or duration-related. Thus, the objective of this review was to systematically evaluate the literature to determine whether a relationship exists between neutropenia and vancomycin dose or duration and to provide the clinician with feasible treatment alternatives.

Data Sources and Selection

A systematic literature search of English language articles in PubMed (1949-November 2010), MEDLINE (1950-November 2010), EMBASE (1980-November 2010), and *International Pharmaceutical Abstracts* (1970-November 2010) was performed using the following terms: vancomycin, neutropenia, and leukopenia. Bibliographies of all articles retrieved from the search were reviewed for additional reports not captured initially. Studies and case reports were included in our review if they reported neutropenia with intravenous or intraperitoneal vancomycin administration. Studies and reports were excluded from this review if they did not describe vancomycin dosages and/or concentrations or if neutropenia resolved while the patient was still receiving vancomycin. Cases in which significant confounders may have resulted in neutropenia and those in which authors provided minimal information about patients were also excluded. We assessed all cases of neutropenia for strength of association with vancomycin by using the Naranjo probability scale, which has been demonstrated to be a reliable and valid scale in determining the probability of an adverse drug event occurring due to a particular drug.[11] All studies that met the inclusion criteria were assessed in this review and were not excluded based on their Naranjo scores.

Seven retrospective case series (ie, chart reviews) and 34 case reports were identified through the literature search. Three retrospective case series and 26 case reports met our inclusion criteria and are described below (Figure 1).[5,6,10,12-37] Two case series and 6 case reports were excluded from the review, because dosages were not reported.[8,38-44] One retrospective case series was excluded, due to a large discrepancy in baseline neutrophil counts between cases and controls (1600/µL vs 8000/µL), with cases having a neutrophil count below the lower limit of normal. This potential confounder limited our ability to determine any association between vancomycin dosing and the development of neutropenia.[7] An additional retrospective chart review of a patient with leukopenia was excluded, because the patient's white blood cell (WBC) count recovered with continued vancomycin administration; therefore, vancomycin was unlikely to be the cause of the leukopenia.[45] Two final case reports were excluded from our review due to limited information provided by the authors.[46,47]

Literature Review

RETROSPECTIVE CASE SERIES

The first published retrospective chart review by Dangerfield and colleagues[5] was designed to assess the clinical use of vancomycin. Vancomycin-associated neutropenia was identified in 2 of the 85 charts reviewed (reported incidence of 2%). Cases were briefly described and details are reported in Table 1. The daily doses of vancomycin ranged from 1.5 to 2 g, with a total vancomycin exposure of 13.5 to 46 g. Vancomycin concentrations were not reported. Concomitant medications were not reported in this retrospective study; therefore, other potential medication-related causes cannot be ruled out. The duration of vancomycin therapy was 9-23 days and time to recovery after vancomycin discontinuation was 1-4 days. Based on the Naranjo probability scale, the association of vancomycin with neutropenia in both cases was categorized as possible.

A chart review by Morris and Ward[6] in 1991 assessed the incidence of vancomycin-associated leukopenia and neutropenia. Of 49 patients on a cardiothoracic surgical ward, 3 (6%) developed leukopenia alone (WBC <4000/µL, as de-

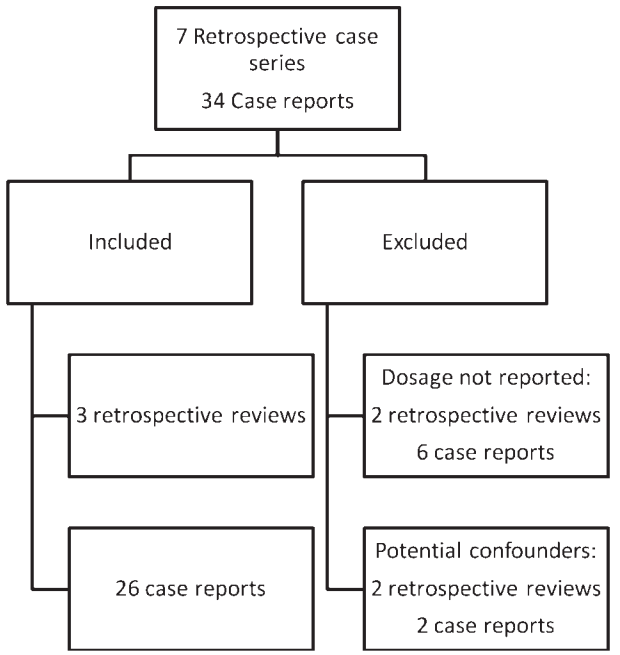

Figure 1. Search strategy flow diagram: inclusion and exclusion of retrospective case series and case reports.

fined by the authors) and 6 (12%) had neutropenia (ANC <1500/μL, as defined by the authors). Of the neutropenic cases, 4 (8%) were described as severe (ANC <1000/μL). The individual cases are summarized in Table 1. Daily dosages of vancomycin were not reported; however, total exposure to vancomycin ranged from 22 to 56 g. Vancomycin concentrations were assessed, on average, 1.5 times per week, and trough concentrations ranged from 3 to 13 mg/L. Duration of vancomycin use ranged from 12 to 28 days. Concomitant drugs that may have confounded the results were reported. Details regarding when these medications were started and stopped in relation to the leukopenia or neutropenia were not described, making it difficult to determine their role, if any, in lowering WBC and neutrophil counts. All patients had recovery of their WBC and ANC counts within 11 days after vancomycin was discontinued. The cases of neutropenia were categorized as possible, according to the Naranjo probability scale.

In 2009, Hung and colleagues[12] retrospectively assessed the cross-reactivity between vancomycin and teicoplanin by examining patients who developed neutropenia, rash, or drug-induced fever while receiving vancomycin and their tolerance to teicoplanin. Teicoplanin is a glycopeptide, which is similar in structure to vancomycin and consequently has the potential to cross-react with vancomycin.[36] Eight patients with vancomycin-induced neutropenia (ANC <1500/μL, as defined by the authors) were included in this review. Four of the patients later developed teicoplanin-induced neutropenia. Of these 4 patients, total daily dosages of vancomycin ranged from 1 to 2.25 g, and cumulative doses ranged from 17 to 47.3 g. No vancomycin concentrations were reported, and concomitant medications were not documented. Patients were treated with vancomycin for 7-21 days and recovery from the neutropenic episode occurred between 4 and 7 days. Data on the remaining 4 patients who developed vancomycin-induced neutropenia, but not teicoplanin-induced neutropenia, were not reported. It is beyond the scope of this review to address the association of teicoplanin with neutropenia; however, this report[12] does suggest that patients who develop vancomycin-induced neutropenia may exhibit a similar reaction with teicoplanin. The vancomycin-induced neutropenia cases are summarized in Table 1. Hung and colleagues assessed the probability of vancomycin causing neutropenia in these patients with the Naranjo probability scale and found a probable association.

Case Reports

The case reports are summarized in Table 2.[5,6,10,12-37] Patient ages ranged from 1 to 74 years. Treatment with vancomycin was initiated for a range of indications, including endocarditis, soft tissue infections, osteomyelitis, bacteremia, infected prostheses, and pneumonia. Patients received a wide variety of dosages, with total exposures ranging from 2.3 to 111 g. Patients in whom a vancomycin concentration was reported had trough concentrations ranging from 4.7 to 10.1 mg/L[10,23,27,30] and random concentrations of 3.2-21.4 mg/L.[18,24,35] All patients had an onset to neutropenia and time to nadir of at least 10 days, with the majority of cases occur-

Table 1. Vancomycin-Induced Neutropenia: Summary of Retrospective Case Series

Reference	Age (y), Sex	Indication	Vancomycin Dose/Day (g)	Total Cumulative Dose (g)	Vancomycin Trough Level (mg/L)	Duration of Vancomycin Use (days)	ANC Nadir (/μL)	Time to Recovery (days)	Strength of Association[a]
Dangerfield	29, M	Wound infection	2	46	NR	23	400	4	Possible
(1960)[5]	32, F	Wound infection	1.5	13.5	NR	9	100	1	Possible
Morris	27, F	NR	NR	30	13	22	780	11	Possible
(1991)[6]	56, M	NR	NR	41	7	28	1120	4	Possible
	33, M	NR	NR	47	8-11	25	1590	4	Possible
	29, F	NR	NR	28	9-12	19	2770	4	Possible
	32, F	NR	NR	56	3	28		9	Possible
	64, M	NR	NR	28	NR	15	<1500	4	Possible
	30, M	NR	NR	22	7-13	12		5	Possible
	24, M	NR	NR	34	8	23		4	Possible
	27, M	NR	NR	24	4	14		1	Possible
Hung	NR	NR	2	17	NR	7		5	Probable
(2009)[12]	NR	NR	2	32	NR	16		4	Probable
	NR	NR	1	19	NR	19		5	Probable
	NR	NR	2.25	47.3	NR	21		7	Probable

ANC = absolute neutrophil count; NR = not reported.
[a]According to Naranjo probability scale[10]; all doses were administered intravenously unless otherwise stated.

Table 2. Vancomycin-Induced Neutropenia: Summary of Case Reports

Reference	Age (y), Sex	Indication	Vancomycin Dose/Day (g)	Total Cumulative Dose (g)	Vancomycin Trough Level (mg/L)	Time to Nadir (days)	ANC Nadir (/μL)	Time to Recovery (days)	Strength of Association[a]	Potential Contributing Drugs	Comments
Borland (1979)[13]	10, F	Endocarditis	1	35	NR	35	500	3	Probable		
Kesarwala (1981)[14]	11, F	Soft tissue infections, bacteremia	40 mg/kg/day every 6 h	Not able to calculate	NR	30	480	1	Probable		
West (1981)[15]	61, M	Osteomyelitis	1.5-2	70	NR	39	330	NR	Probable		
Kauffman (1982)[16]	55, M	Osteomyelitis, endocarditis	2	62	NR	31	440	6	Probable		
Strikas (1982)[17]	48, M	Bacteremia	1-2	Not able to calculate	NR	15	1400	5	Probable		
	32, M	Endocarditis	2-3	Not able to calculate	NR	34	190	7	Possible	Furosemide	Nadir occurred 4 days after stopping vancomycin
Farwell (1984)[18]	55, M	Cellulitis	1 g weekly × 4	4	3.2 (random)	50	0	15	Possible		Dialysis pt. developed neutropenia 1 mo after last dose
Mackett (1985)[19]	67, F	Cellulitis, bacteremia	0.5	9.5	NR	19	1200	5	Probable		
Adrouny (1986)[20]	40, M	Cellulitis	1 g weekly × 3	3	NR	28	NR	NR	Possible		WBC nadir 200/μL
Koo (1986)[21]	59, F	Infected hip prosthesis	1-2	54	NR	33	NR	7	Possible	Phenyl-butazone	Pt. tolerated re-exposure to vancomycin × 5 days
Mordenti (1986)[22]	37, M	Bacteremia	1.5-2	32.5	NR	20	0	3	Doubtful	Mezlocillin, tobramycin	Vancomycin stopped days 11-13
Henry (1986)[23]	50, M	Osteomyelitis	2	38	10.1	19	150	13	Possible	Hydrochlorothiazide triamterene	
Milsteen (1987)[24]	35, M	Fistula site infection	0.8 g × 1, 0.5 g × 1, 1 g × 1	2.3	21.4 (random)	35	0	34	Probable		Dialysis pt.
Domen (1990)[25]	36, M	Endocarditis	2	56	NR	27	0	13	Possible	Rifampin	
Comer (1992)[26]	74, M	Endocarditis	1-1.2	26.2	NR	26	130	4	Probable		
Shinohara (1994)[27]	2, M	Endocarditis	1	Not able to calculate	5-10	18	460	5	Possible		Slightly pancytopenic on admission
Lai (1996)[28]	37, M	Infected knee	2-3.4	83	NR	NR	480	3	Possible	NR	Given G-CSF to complete vancomycin course
Lai (1996)[28]	33, M	Osteomyelitis	2	30	NR	15	860	NR	Possible	NR	Given G-CSF to complete vancomycin course
Shuster (1997)[29]	25, F	Wound infection	2	58	NR	30	280	3	Possible	Ampicillin-sulbactam	

Mandl (1997)[30]	45, F	Osteomyelitis, wound infection	1-2.4	33.4	8.2	20	80	NR	Possible	Ticarcillin-clavulanate	
Smith (1999)[31]	39, F	Osteomyelitis	2	24	NR	12	240	3	Probable		
Shahar (2000)[32]	43, F	Wound infection	NR	28	NR	14	1610	4	Possible	Ceftazidime	Vancomycin stopped days 10-12
Sanche (2000)[33]	35, M	Osteomyelitis	3	111	NR	37	610	8	Probable		Pt. tolerated teicoplanin
Rocha (2002)[34]	60, F	Infected hip prosthesis	2	50	NR	25	160	2	Possible		
	38, F	Infected hip prosthesis	2	20	NR	10	1260	4	Possible	Cefepime, imipenem	
Segarra-Newnham (2004)[10]	64, M	Osteomyelitis	1.5	34.5	4.7	23	420	7	Probable		
Jo (2004)[35]	66, M	Pneumonia, catheter infection	1 g IP weekly	11.0	17.5 (random)	82	0	3	Possible	Aztreonam, ceftazidime	
Hsiao (2007)[36]	57, F	Osteomyelitis	2.25 (from day 9)	Not able to calculate	NR	24	280	6	Probable		Neutropenia recurred with exposure to teicoplanin
Lee (2009)[37]	1, M	Sepsis	50 mg/kg/day	Not able to calculate	NR	23	490	10	Possible	Amoxicillin-clavulanate, tobramycin	Nadir occurred 4 days after vancomycin discontinued

ANC = absolute neutrophil count; G-CSF = granulocyte colony-stimulating factor; IP = intraperitoneal; NR = not reported; WBC = white blood cell.
[a]According to Naranjo probability scale[10]; all doses were administered intravenously unless otherwise stated.

ring at 20 days or beyond.[10,13-18,20-22,24-26,29,30,33-37] Many patients received concomitant medications when they developed neutropenia. Medications that were continued throughout the recovery phase were unlikely to contribute to the neutropenia (given that a temporal relationship did not exist) and therefore are not listed in Table 2. Although there was a sequential relationship between initiation and discontinuation of vancomycin with the onset and resolution of neutropenia, case reports are limited by potential confounders and biases, which should be considered when determining a direct association between vancomycin and the development of neutropenia. The strength of the association between vancomycin and neutropenia was categorized as possible or probable, according to the Naranjo probability scale for all case reports, with the exception of 1 case report rated as doubtful. The case report by Mordenti and colleagues[22] was categorized as doubtful due to baseline neutropenia and administration of concomitant medications that may have contributed to neutropenia.

Discussion

Several published retrospective studies and case reports document neutropenia as an adverse event associated with intravenous and intraperitoneal vancomycin use; however, there are no prospective studies published to date assessing this important clinical complication. Chart reviews and case reports identified in this systematic search suggested that neutropenia may occur over a wide range of dosages and total cumulative dosages. Furthermore, the evidence consistently demonstrated that the onset of vancomycin-induced neutropenia occurred with prolonged use.

Daily vancomycin dosages ranged from 250 mg twice daily to 1700 mg twice daily in patients with normal renal function and 1000 mg weekly in hemodialysis patients (with a total cumulative dose ranging from 2.3 to 111 g). Although there was significant variability in dosages administered, the highest vancomycin trough concentration was 10.1 mg/L and the highest random concentration was 21.4 mg/L.[23,24] These findings suggest that vancomycin-induced neutropenia may not be completely related to daily dosages, total cumulative dosage, or supratherapeutic concentrations. However, these reports do suggest that neutropenia is more likely associated with prolonged therapy. Specifically, our review showed that vancomycin-induced neutropenia occurred after a minimum of 7 days, with the majority of cases occurring at least 20 days after initiation of therapy.

IMMUNE-MEDIATED NEUTROPENIA

The exact mechanism of vancomycin-induced neutropenia is unknown; however, an immunologic mechanism has been proposed. Weitzman and Stossel[44] were the first to address this question and evaluated drug-induced neutropenia (defined as ANC <1000/μL) in 3 patients receiving vancomycin and cephalosporins. The authors reported the detection of opsonising antineutrophil antibodies, indicating the possibility of an IgG or IgM immune-mediated hypersensitivity reaction. The potential for the development of antineutrophil antibodies and resultant neutropenia from the concomitant cephalosporins cannot be ruled out, given that antibodies were also detected in neutropenic patients receiving monotherapy with penicillins.

Further evidence to support an immunologic hypothesis was demonstrated by Domen and Horowitz.[25] Bone marrow examination of a patient with vancomycin-induced neutropenia (and concomitant rifampin) showed granulocyte-specific antibodies. Schwartz[38] reported a case in which bone marrow biopsy revealed decreased myeloid precursors and granulocyte antibodies. In addition, the patient developed a maculopapular rash in the presence of vancomycin, imipenem-cilastatin, ciprofloxacin, and acyclovir, further supporting the hypothesis of a hypersensitivity reaction. These concomitant medications may have been contributing factors to the development of these antibodies. Antineutrophil antibodies were also detected in the serum of a 22-month-old child who was thought to have vancomycin-induced neutropenia.[37] As in previous reports, this patient was concomitantly taking other antibiotics, including a cephalosporin and roxithromycin. After the child developed a maculopapular rash and neutropenia, these medications were replaced with amoxicillin-clavulanate and gentamicin. On further assessment of autoantibodies to antibiotics, antibodies specific for cefotaxime, amoxicillin-clavulanate, vancomycin, and tobramycin were present. A bone marrow aspirate was not obtained.

Several other case reports add weight to the hypothesis that vancomycin-induced neutropenia is immune-mediated. West[15] reported a case of vancomycin-induced neutropenia in which a bone marrow biopsy demonstrated normal myeloid precursors with slight hypocellularity. These authors did not assess the patient for antineutrophil antibodies; however, given normal myeloid precursors, a toxic effect on bone marrow is not likely. Mackett and Guay[19] observed peripheral lymphocyte transformation on exposure to vancomycin at therapeutic concentrations. The authors concluded that these findings were suggestive of an immune-mediated reaction; however, bone marrow aspirates and antibody testing were not performed. Kauffman and colleagues[16] assessed a bone marrow aspirate of a patient considered to have vancomycin-induced neutropenia and found hypercellularity of granulocyte cells with normal maturation. Antibodies active against neutrophils were assessed by several methods but were not detectable. Although antibodies were not identified, there did not appear to be a direct toxic effect on the bone marrow.

DIRECT TOXICITY ON BONE MARROW

Other researchers have proposed a direct toxic effect on bone marrow as a potential mechanism of vancomycin-induced neutropenia.[5,20,22,24] Dangerfield and colleagues[5] assessed bone marrow in a patient with vancomycin-induced neutropenia and reported maturation arrest of the granulocyte series. Two case reports on hemodialysis patients also showed myeloid hypoplasia on assessment of the bone marrow.[20,24] In 1 case, serum testing did not demonstrate drug-dependent leuko-agglutinating antibodies.[24] A final case report by Mordenti and colleagues[22] had similar findings in a patient with leukemia demonstrating decreased granulocyte cells on bone marrow biopsy. The authors stated that other recognized causes of neutropenia were excluded by appropriate studies.

Both a direct toxic effect on bone marrow and an immune-mediated mechanism support the hypothesis that vancomycin-induced neutropenia is related to total exposure and duration of vancomycin use. A type I IgE-mediated hypersensitivity reaction is unlikely due to the delayed nature of this reaction; however, the possibility of a type II IgG- or IgM-mediated hypersensitivity reaction exists. Continued exposure for longer periods is also in keeping with a direct toxic effect on the bone marrow. Onset of neutropenia with vancomycin is similar to that in a report of neutropenia associated with β-lactam antibiotics that had a delayed onset of 21 days. Both an IgG-mediated reaction and direct toxic effects on the bone marrow were postulated as potential mechanisms of β-lactam–induced neutropenia in this prospective study.[48]

CLINICAL IMPLICATIONS

Vancomycin-induced neutropenia is a serious adverse reaction associated with potential morbidities and increasing risk of infection. Close monitoring needs to be considered if therapy is to continue for a prolonged duration. As noted, episodes of neutropenia may occur as early as 7 days, while the majority appear to develop beyond 20 days. Given these findings, a practical approach would be to monitor the WBC count with a differential count (including ANC) once a week in patients who are receiving vancomycin for more than 7 days.

When neutropenia is suspected, an extensive assessment for drug- and nondrug-related causes should be performed. If there is a high clinical suspicion that the neutropenia is

caused by vancomycin, the drug should be discontinued and an alternative agent should be initiated. The use of granulocyte colony-stimulating factor (G-CSF) for the treatment of vancomycin-induced neutropenia remains controversial. There are 2 case reports of successful treatment of vancomycin-induced neutropenia with G-CSF; however, further evaluation is needed before this combination can be recommended.[28] Currently, no guidelines or recommendations are available for the use of G-CSF or other growth factors in the management of vancomycin-induced neutropenia. At this time, it is unclear whether patients with previous vancomycin-induced neutropenia would develop the same neutropenic response if rechallenged with vancomycin in a subsequent infectious episode. In most cases, clinicians would avoid vancomycin and use an alternative agent. Further studies are required to determine the likelihood of neutropenia with repeat exposure to vancomycin.

TREATMENT ALTERNATIVES

Vancomycin remains one of the most widely used antibiotics for the treatment of *Staphylococcus* (including methicillin-resistant *Staphylococcus aureus*), *Streptococcus*, and *Enterococcus* infections. Treatment alternatives to vancomycin that provide gram-positive coverage are listed in Table 3.[49-54]

LIMITATIONS

Several limitations exist in our systematic review. Retrospective chart reviews and case reports are subject to publication bias and only serve to hypothesize a potential relationship between dosage and duration with neutropenia, but a direct causal association cannot be clearly established. Confounders that are present in this analysis include the range in details reported, concomitant medications that may have contributed to the neutropenia, and comorbid conditions that may have predisposed the patients to neutropenia. Vancomycin concentrations were not reported uniformly, and the level at the time of neutrophil nadir was not always reported, which would affect the interpretation of the correlation between vancomycin concentration and neutropenia. Furthermore, the definition of vancomycin-induced neutropenia varied between studies, limiting our ability to directly compare results. Finally, it remains unclear whether the cause of vancomycin-induced neutropenia is due to the drug itself or to the impurities in the formulation. In a recent study, Vesga and colleagues[55] compared several generic versions of intravenous vancomycin to the brand name product (innovator). The generic products were found to have similar pharmacokinetic and in vitro characteristics to the innovator, but lacked in vivo activity when compared to the innovator. The authors suggested that the generic formulations may contain inhibitory and stimulatory factors that may have contributed to the in vivo failure. With the availability of different generic vancomycin products and formulations, the ability to identify a causative agent for vancomycin-induced neutropenia may become even more complex as the differences in the formulations may lead to variations in the incidences of neutropenia. Despite these limitations, retrospective reviews and case reports do provide valuable information to address potential risk factors for vancomycin-induced neutropenia.

Summary

From the available data, vancomycin-induced neutropenia is most likely associated with prolonged exposure and generally occurs at least 20 days after initiation of treatment. Patients who receive vancomycin for more than 7 days should have WBC and differential counts monitored weekly. Vancomycin should be discontinued if there is a high clinical suspicion of it causing neutropenia, and an alternative agent should be initiated. Prospective case-controlled studies are needed to better characterize this adverse event.

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Table 3. Treatment Alternatives to Vancomycin for Gram-positive Coverage

Antibiotic (class)	Dose	Mechanism of Action	Gram-Positive Coverage	Indications	Comments
Ceftaroline (5th generation cephalosporin)[49]	600 mg iv every 12 h	Binds to penicillin binding protein and inhibits peptidoglycan synthesis (bactericidal)	*Staphylococcus* (including MRSA), *Streptoccocus*, gram-negatives (not *Pseudomonas*)	Skin and skin structure infections, community-acquired pneumonia	Approved by the FDA October 2010
Clindamycin (lincosamide)[49-51]	150-600 mg po/iv every 6-8 h	Binds 23S portion of 50S subunit of bacterial ribosomes; dissociates peptidyl-transfer RNA from ribosome (bacteriostatic)	*Staphylococcus aureus* (including community-associated MRSA), *Streptococcus*, *Peptostreptococcus*, and anaerobes	Skin and skin structure, bone and joint, respiratory tract, intraabdominal and gynecologic infections	Resistance against Staphylococcus and Streptococcus increasing; use should be based on local susceptibilities and culture results; oral bioavailability 90%; oral dosage form should be used unless absorption is an issue
Co-trimoxazole trimethoprim-sulfamethoxazole (sulphonamide)[49-51]	trimethoprim 8-20 mg/kg/day po/iv divided 6-12 h	Trimethoprim and sulfamethoxazole synergistically inhibit folate synthesis (bactericidal)	*Staphylococcus* (including susceptible strains of MRSA); in vitro activity against *Streptococcus*, but not clinically effective against group A *Streptococcus*; exhibits some gram-negative activity	Skin and skin structure, respiratory tract and urinary tract infections	Bone marrow suppression occurs rarely
Daptomycin (lipopeptide)[49,51,52]	4-6 mg/kg iv daily	Binds and depolarizes bacterial cell membrane (bactericidal)	*Staphylococcus* (including MRSA), Streptococcus, *Enterococcus* (including vancomycin-resistant *Enterococcus*	Skin and skin structure infections, bacteremias, right-sided staphylococcal (including MRSA) endocarditis	Inactivated by surfactants in the lungs; ineffective for treatment of pneumonia; adverse effects include increased creatinine kinase and eosinophilic pneumonia; weekly creatinine kinase monitoring recommended
Doxycycline (tetracycline)[49,50]	100-200 mg/day po/iv divided every 12-24 h	Binds 30S and possibly 50S bacterial ribosomal subunits and inhibits protein synthesis (bacteriostatic)	*Staphylococcus* (including MRSA) and *Streptococcus*; exhibits some gram-negative and atypical coverage	Community-acquired MRSA skin and skin structure infections,community-acquired pneumonia	Administration on empty stomach (1 h before or 2 h after meals) preferred to maximize absorption; avoid in children under 8 y (may cause permanent tooth discoloration); avoid unnecessary exposure to sunlight due to photosensitivity
Linezolid (oxazolidinone)[49,51]	400-600 mg po/iv every 12 h	Binds to 23S ribosomal RNA of 50S subunit; prevents formation of 70S initiation complex in bacterial translation, inhibits protein synthesis (bacteriostatic)	*Staphylococcus* (including MRSA) and *Enterococcus* (including vancomycin-resistant *Enterococcus*); bactericidal against most strains of *Streptococcus*	Skin and skin structure infections, community-acquired and nosocomial pneumonias, bacteremia	Thrombocytopenia reported in up to 10% of pts.; weekly monitoring of complete blood counts recommended if treatment >2 wk
Quinupristin-dalfopristin (streptogramin)[49,51,53]	7.5 mg/kg iv every 8-12 h	Inhibits protein synthesis by binding to 50S ribosomal subunit (bacteriostatic individually; bactericidal in combination)	*Staphylococcus* (including MRSA), *Streptococcus*, *Enterococcus faecium* (including vancomycin- resistant *Enterococcus faecium*) but not *Enterococcus faecalis*	Skin and skin structure infections, bacteremia, vancomycin-resistant *Enterococcus faecium* infections	Common adverse effects include arthralgias and myalgias, occurring in up to 47% of pts.
Tigecycline (glycylcycline)[49,51,54]	100 mg iv loading, 50 mg iv every 12 h	Binds to 30S ribosomal subunit and inhibits protein synthesis (bacteriostatic)	*Staphylococcus* (including MRSA), *Streptoccocus*, *Enterococcus* (including vancomycin-resistant *Enterococcus*), gram-negatives (not *Pseudomonas*), anaerobes	Skin and skin structure infections, community-acquired pneumonia, intraabdominal infections	For serious infections, the FDA recommends alternative antimicrobials, as there may be increased mortality risk with tigecycline; nausea is most common adverse effect

FDA = Food and Drug Administration; MRSA = methicillin-resistant *Staphylococcus aureus*.

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Neutropenia Inducida por Vancomicina: ¿Relacionada a la Dosis o a la Duración?

E Black, TTY Lau, y MHH Ensom

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EXTRACTO

OBJETIVO: Evaluar la literatura sistemáticamente para determinar si la neutropenia inducida por vancomicina está relacionada a la dosis o a la duración y proveer al personal clínico alternativas viables de tratamiento.

FUENTES DE DATOS: Una búsqueda en PubMed (1949 – noviembre de 2010), MEDLINE (1950 – noviembre de 2010), Embase (1980 – noviembre de 2010) e *Abstractos Farmacéuticos Internacionales* (1970 – noviembre de 2010) fue llevada a cabo usando los siguientes términos: vancomicina, neutropenia, y leucopenia. Citaciones de publicaciones fueron revisadas para referencias adicionales.

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Estudios y reportes de casos fueron incluidos si reportaban neutropenia con la administración de vancomicina y eran excluidos si no describían las dosis o los niveles de vancomicina, o si la neutropenia se revertía mientras el paciente estaba en vancomicina. Casos con factores significantes confusos y los que proveían poca información sobre los pacientes fueron excluidos.

SÍNTESIS DE DATOS: Siete revisiones retrospectivas de historiales médicos (series de casos) y 33 reportes de casos fueron identificados. De estos, 3 revisiones retrospectivas y 26 reportes de casos cumplieron con los criterios de inclusión. Para nuestro conocimiento, ningún estudio prospectivo ha evaluado esta complicación clínica. Los datos sugieren que la neutropenia inducida por vancomicina no está completamente relacionada a las dosis diarias, dosis total acumulada, o niveles supraterapéuticos de vancomicina. Además, la evidencia sugiere que la neutropenia está posiblemente asociada más con terapia prolongada mayor de 7 días, con la mayoría de los episodios ocurriendo después de 20 días de terapia. Dado estos hallazgos, un enfoque práctico es monitorear el nivel de células blancas con diferencial (incluyendo nivel absoluto de neutrófilos) una vez a la semana en pacientes que están recibiendo vancomicina por más de 7 días.

CONCLUSIONES: La neutropenia inducida por vancomicina está posiblemente asociada a la exposición prolongada a vancomicina y generalmente ocurre por lo menos 20 días después del inicio del tratamiento. Los pacientes que reciban vancomicina por más de 7 días deben tener un nivel y diferencial de células blancas semanalmente. Vancomicina debe ser descontinuada si hay sospechas de que está causando neutropenia y se debe iniciar un agente alternativo. Más estudios prospectivos controlados de casos son necesarios para caracterizar mejor este evento adverso.

Traducido por Sonia I Lugo

Neutropénie Induite par la Vancomycine: Liée à la Dose ou à la Durée de Traitement?

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RÉSUMÉ

OBJECTIF: Évaluer systématiquement la littérature médicale pour déterminer si la neutropénie induite par la vancomycine est liée à la posologie ou à la durée de traitement, et fournir aux cliniciens des alternatives de traitement.

REVUE DE LA LITTÉRATURE: Une recherche dans la base de données informatisée PubMed (1949-novembre 2010), MEDLINE (1950-novembre 2010), Embase (1980-novembre 2010), et *International Pharmaceutique Résumé* (1970-novembre 2010) a été faite en utilisant les mots-clé: vancomycine, neutropénie, et leucopénie. Les articles citées en référence ont aussi été pris en considération.

SÉLECTION DES ÉTUDES ET DE L'INFORMATION: Les études et les rapports de cas ont été inclus dans cet article si la mention neutropénie lors d'administration de vancomycine était présente; ils étaient exclus si les niveaux et les doses de vancomycine n'étaient pas bien décrits ou si la neutropénie a été résolue alors que le patient était toujours sous vancomycine. Les cas où d'autres facteurs pouvaient être responsables de la neutropénie ou encore si l'information était insuffisante étaient aussi exclus.

SYNTHÈSE DES DONNÉES: Sept revues rétrospectives de dossier (séries de cas) et 33 rapports de cas ont été identifiés. De ce total, 3 revues rétrospectives et 26 rapports de cas remplissaient les critères d'inclusion. Selon les auteurs, aucune étude prospective n'a évalué cette complication clinique de la vancomycine. Les données suggèrent que la neutropénie induite par la vancomycine n'est pas totalement liée au dosage quotidien, à la dose cumulative totale ou à des niveaux supra-thérapeutiques de vancomycine. Des données additionnelles suggèrent que la neutropénie est liée à des durées de traitement de plus de 7 jours, la majorité des épisodes de neutropénie survenant après 20 jours de traitement. D'après ces données, une approche pratique serait de faire la numération des globules blancs et la numération leucocytaire différentielle, incluant la valeur absolue des neutrophiles, à chaque semaine chez les patients qui reçoivent de la vancomycine pour une durée de traitement de plus de 7 jours.

CONCLUSIONS: La neutropénie induite par la vancomycine semble associée à une exposition prolongée et survient généralement au moins après 20 jours de traitement. On devrait faire la numération des globules blancs et la numération leucocytaire différentielle, incluant la valeur absolue des neutrophiles, à chaque semaine. La vancomycine devrait être cessée si on suspecte grandement qu'elle est responsable de neutropénie, et un autre agent anti-infectieux devrait être prescrit. Des études prospectives contrôlées sont nécessaires pour mieux définir cet effet indésirable de la vancomycine.

Traduit par Denyse Demers