한국임상약학회지 제23권 제1호
Kor. J. Clin. Pharm., Vol. 23, No. 1. 2013

반코마이신 단기간 투여로 유발된 호중구감소증 증례보고

김수현[1] · 방준석[2] · 김광준[2] · 이유정[3*]
[1]가톨릭대학교 여의도성모병원 약제팀, [2]조선대학교 약학대학, [3]강원대학교 약학대학

(2012년 8월 25일 접수 · 2013년 2월 19일 수정 · 2013년 2월 22일 승인)

A Case of Neutropenia Induced by Short-Term Treatment of Vancomycin

Su Hyun Kim[1], Joon Seok Bang[2], Kwang Joon Kim[2], and Yu Jeung Lee[3]*
[1]*Department of Pharmacy, Yeoido St. Mary's Hospital, Seoul, Korea*
[2]*Department of Clinical pharmacy, College of Pharmacy, Chosun University, Gwangju, Korea*
[3]*Department of Clinical pharmacy, College of Pharmacy, Kangwon National University, Gangwon-do, Korea*

(Received August 25, 2012 · Revised February 19, 2013 · Accepted February 22, 2013)

메치실린 저항성 황색 포도상구균(MRSA)에 감염된 환자에게 단기간 연속적으로 반코마이신을 투여했을 때 비정상적으로 호중구의 수치가 감소한 약인성 부작용 사례를 보고하고자 한다. 해당 여성 환자는 61세로서 MRSA 감염증을 판정받고 반코마이신 투여와 더불어 점차 백혈구(WBC)와 절대호중구수치(ANC)가 감소하였고, 제10일째에 이르러 호중구감소증이 발생하여 ANC가 최저 430 cells/mm^{3}까지 낮아졌으나, 반코마이신의 투여를 중단하자 곧 정상수준으로 회복되었다. 본 사례는 Naranjo Probability Scale과 Korean Algorithm Score(Ver. 2.0)로 각각 평가하였을 때 반코마이신의 투여와 호중구감소증의 발현 사이에 모두 '가능한(probable)' 정도의 인과관계를 가진 것으로 평가되었다. 이는 통상적으로 20일 이상 연속투여를 할 때 임상적으로 관측되던 반코마이신-유래 호중구감소증이 단지 10일 정도의 단기간 투여만으로도 발생할 수 있다는 임상적 약물부작용의 사례로서, 향후 MRSA환자에게 반코마이신을 선택할 때에는 이와 같은 부작용을 고려하여 환자의 WBC와 ANC를 면밀히 관찰하면서 투여할 필요성이 있음을 시사한다.

□ Key words - Bacteremia, MRSA, Neutropenia, Vancomycin

INTRODUCTION

Vancomycin (VCM) is a tricyclic glycopeptide antibiotic isolated from *Amycolatopsis orientalis*. VCM has an antibacterial effect on a wide range of Gram-positive bacteria, and it is used as the primary choice on methicillin-resistant *Staphylococcus aureus* (MRSA), *Corynebacterium jeikeium*, *Pseudomembranous colitis*, and *Streptococcus pneumoniae.* Also VCM is selected as an alternative for the patients showing allergic reaction to penicillin or cephalosporin analogs. VCM mainly represents the bactericidal activities by inhibiting the synthetic pathways of the cell wall of the pathogens, and the direct intravenous route is favored against the systemic infections because its oral bioavailability is less than 5%. Especially, VCM can be accumulated in the patients whose renal function are diminished and even cause toxic reactions, so careful dosage adjustment is necessary.[1-5)]

As the frequency of VCM use increased, reports of drug-induced adverse reactions (ADRs) have also soared. The most common (> 10%) ADRs are hypotension and Red-man's syndrome. Other ADRs, including ear toxicity, thrombocytopenia, renal failure, and hematologic defects are rarely reported.[2,4)]

Neutropenia is defined as an absolute neutrophil count (ANC) less than 1500/mm^3, typically classified as mild (1000~1500/mm^3), moderate (500~1000/mm^3), and severe

Correspondence to : Yu Jeung Lee
College of Pharmacy, Kangwon National University, Chuncheon-si, Gangwon-do 200-701, Korea
Tel: +82-33-250-6913, Fax: +82-33-255-7865
E-mail: yujeung@kangwon.ac.kr
※The first and second authors contributed equally to this manuscript.

(about 500 or more/mm^3).[6] Neutropenia is caused by decrease in neutrophil formation from bone marrows; inefficiency of granulocyte hematopoiesis; and increase in peripheral destruction. When ANC decreases, risks for pathogenic infection of the host body increase.[7] Neutropenia, an ADR associated with VCM has been reported very rarely. It is reported that neutropenia occurred regardless of VCM dose, but it was associated with long-term consecutive treatments (over 20 days).[8,9] We describes neutropenia occurred after 10 days of VCM therapy. To the best of our knowledge, this is a rare case based on published literatures.

CASE REPORT

A 61-year-old Korean female was diagnosed as multiple myeloma (Durie-Salmon Stage III) at a tertiary hospital on August 20, 2010. Her height was 151.1 cm and weight was 66.7 kg. She was discharged after receiving high-dose dexamethasone 4 times during hospitalization (through August 23 to 26, August 30 to September 2, September 6 to 9, and October 1 to 3, respectively). Two years ago she got diagnosed as hypertension at a primary care clinic and has been receiving amlodipine (5 mg), olmesartan (20 mg), aspirin (100 mg) once a day. She was also previously diagnosed as multiple myeloma at other tertiary institution and has been taking amlodipine (5 mg), candersartan (6 mg), folic acid (1 mg), and oxycodone (10 mg) once a day, and magnesium hydroxide (500 mg) 3 times a day. She did not smoke, drink alcohol, or exercise regularly.

On October 18, 2010, she was admitted to the emergency department at a tertiary hospital with consistent nausea, abdominal pain, chills, and diarrhea which occurred after eating simmered cutlass fish for the last dinner (around 2 AM on October 18). Physicians suspected urinary tract infection and administered ciprofloxacin 200 mg twice a day for 3 days, but the result of microbiologic test on 5th day of hospitalization proved MRSA bacteremia and the current antibiotics were changed immediately to VCM 1 g twice a day and gentamicin 320 mg (5 mg/kg×67 kg) per day in three divided doses.

The patient's White Blood Cell (WBC) and ANC decreased continuously below normal limits and she started complaining weakness and fatigue 3 days after the initiation of VCM and gentamicin, and fevers also occurred on the 5th day of VCM therapy. On November 2, 10 days after the initiation of VCM therapy, neutropenia (ANC is 980/mm^3) was observed. Because her physician suspected that her symptoms and reduced WBC and ANC were caused by the antibiotics that she was taking, VCM was discontinued on the 10th day, and teicoplanin (400 mg) was administered 3 times with 12 hr intervals, then once a day thereafter instead of VCM. Gentamicin had been given to her without any changes. Six days after the discontinuation of VCM, WBC and ANC levels returned to normal. On November 13, WBC and ANC levels returned back to the levels that she had before getting the VCM therapy (Table 1).

Table 1. Changes in vital signs and laboratory values of the patient between before and after vancomycin therapy.

	Day 1	Day 4	Day 7	Day 13	Day 15	Day 16	Day 20	Day 26
SBP/DBP	130/80	110/70	110/60	110/70	100/60	110/60	110/70	100/60
RR	20	20	20	20	20	20	20	22
Temp	37.3	36.5	36.5	37.1	37.5	37.1	37.7	38.4
Cr	1.09	0.87	1.05	1.51	1.75	1.43	1.44	1.47
AST (S-GOT)	23	18	16	21	20	26	13	19
ALT (S-GPT)	23	18	16	15	14	17	14	18
WBC	7.57	6.72	5.63	4.01	2.60	2.05	3.80	8.67
ANC	6.39	5.40	3.12	2.39	0.98	0.43	1.65	6.24

SBP/DBP (systolic blood pressure/diastolic blood pressure, mmHg); RR (respiratory rate, number of breaths per minute); Temp (body temperature, ^oC); Cr (Creatinine, mg/dL); AST (aspartate aminotransferase unit/L); S-GOT (serum glutamate oxaloacetate transaminase, unit/L); ALT (alanine aminotransferase, unit/L); S-GPT (serum glutamate pyruvate transaminase, unit/L); WBC (white blood cell, $10^3/m^3$); ANC (absolute neutrophil count, $10^3/m^3$)

Table 2. The Naranjo Algorithm Score of the case.

Question	Yes	Do not know	No	Score
• Are there previous conclusive reports on this reaction?	+1	0	0	1
• Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
• Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	1
• Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
• Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2
• Did the reaction reappear when a placebo was given?	-1	+1	0	0
• Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
• Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
• Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
• Was the adverse event confirmed by any objective evidence?	+1	0	0	1
Total Score				7
Causality Evaluation				Probable

Highly Probable if the overall score is 9 or greater; *Provable* for a score of 5-8; *Possible* for 1-4; *Doubtful* if the score is 0.

Table 3. The Korean Algorithm (Ver 2.0) Score of the case.

Question			Score	
Chronological relationship	☐ Is there any information on chronological relationship of the suspected drug and ADR?	• Appropriate chronologic relationship	+3	+3
		• Contradictory chronologic relation-ship	-3	
		• No information	0	
Dose reduction or discontinuation	☐ Is there any information on dose reduction or discontinuation?	• Clinical response after dose reduction	+3	+3
		• Clinical progress regardless of dose reduction or discontinuation	-2	
		• No reduction or discontinuation	0	
		• No information	0	
Past ADR history	☐ Have you ever experienced ADR with the same or similar drug?	• Yes	+1	0
		• No	-1	
		• No information	0	
Concomitant medication	☐ Is there any information on drugs being taken concomitantly?	• Cannot explain the association between ADR and the concomi-tant drug	+2	+2
		• Can explain the association between ADR and the concomitant drug	-3	
		• Can explain as interaction between the suspected drug and the concomi-tant drug	+2	
		• No available data on the concomitant drug	0	
		• No information	0	
Non-drug cause	☐ Is there any information on non-drug cause?	• Cannot explain with non-drug cause	+1	0
		• Can explain with non-drug cause	-1	
		• No information	0	
Any known information on the suspected drug	☐ Is there any information on the suspected drug?	• Indicated in approved materials by KFDA (label, insert, etc.)	+3	+3
		• Not indicated, but there are case reports	+2	
		• No information	0	
Re-administration	☐ Is there any information on re-administraion?	• Similar response	+3	0
		• No response	-2	
		• No re-administraion	0	
		• No information	0	
Specific tests	☐ Specific tests such as plasma drug concentration monitoring?	• Positive	+3	0
		• Negative	-1	
		• Unknown results	0	
		• No information	0	
Total Score				11
Causality Evaluation				Probable

Unlikely (≤1); *Possible* (2~5); *Probable* (6~11); *Certain* (≥12); ADR (adverse drug reaction); KFDA (Korea Food and Drug Administration)

DISCUSSION

We conducted a systematic review on VCM-induced neutropenia using databases (MEDLINE 1949~2010; EMBASE 1980~2010; IPA 1970~2010; searching keywords were 'vancomycin', 'neutropenia', and 'leukopenia'), and there was not any evidences suggesting that high plasma concentrations that exceed the therapeutic range, and daily or cumulative dosage of VCM were associated with netropenia. Netropenia was usually observed with long-term treatment of VCM longer than 20 days.[8] However, only 10 days after the initiation of VCM therapy, both WBC and ANC decreased continuously and neutropenia was observed in this case. The renal function of the patient was normal when VCM was started.

It is difficult to consider gentamicin as the cause of neutropenia because the recovery patterns of the patient's WBC and ANC were shown after administration of teicoplanin instead of VCM while continuing gentamicin. In general, regular monitoring of WBC and ANC is recommended if VCM is administered over a long-term period. However, even if the duration of VCM therapy is relatively short, patients receiving VCM require frequent monitoring of WBC and ANC based on this case. If neutropenia occurs during VCM therapy, immediate discontinuation of VCM and use of alternative medications should be considered. In this case, VCM was considered the 'probable' cause of neutropenia according to the 'Naranjo Algorithm'[10] and 'Korean algorithm' (Ver 2.0) (Table 2, Table 3). As there is no established mechanism by which VCM may cause neutropenia, more research is needed. Clinicians should be aware that this potential adverse effect can occur with short-term treatment of VCM when monitoring patients receiving VCM.

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