Original Article

Mahidol Univ J Pharm Sci 2015; 42 (4), 178-185

Prevalence and related factors for injectable vancomycin or teicoplanin-associated thrombocytopenia in a Vietnamese hospital

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Abstract

Thrombocytopenia is a rare but dangerous adverse event when using vancomycin and teicoplanin. The objectives of this study were to evaluate the prevalence and related factors for vancomycin or teicoplanin injection associated thrombocytopenia. We conducted a cross-sectional study based on medical records of all patients aged 18 years and over, who were treated for at least 48 hours with vancomycin or teicoplanin injection at Thong Nhat hospital. Patients using oral vancomycin, or who had blood system disorders or platelet reduction associated with an original disease were excluded from this study. Thrombocytopenia was defined as a decrease in platelet count at least 25% from baseline and lower than 100 x 10^9/L. Thrombocytopenia was observed in 16.2% of patients received vancomycin and 21.9% of patients received teicoplanin (p = 0.292). For vancomycin-associated thrombocytopenia, related factor was sex (male) (OR 5.740; 95% CI 1.155-29.547; p = 0.037) and the appropriateness of drug dosing was a protective factor (OR 0.140; 95% CI 0.031-0.628; p = 0.010). For teicoplanin-associated thrombocytopenia, related factor was treatment in the ICU (OR 5.054; 95% CI 1.077-23.791; p = 0.040) and protective factor was baseline platelet count (≥ 142 x 10^9/L) (OR 0.267; 95% CI 0.087-0.823; p = 0.021). Patients treated with injectable vancomycin or teicoplanin should be monitored the number of platelets before and during treatment to minimize the consequences of thrombocytopenia. Dose adjustment should be considered in patients received vancomycin, especially in male. Teicoplanin should be more carefully indicated in patients in ICU department with a low platelet count.

Keyword: vancomycin injection, teicoplanin injection, thrombocytopenia

1. INTRODUCTION

Antibiotic resistance is a public health concern, and seriously developing. According to a study in 2011 of Ly Ngoc Kinh et al. at some of intensive care units (ICUs) in Vietnam, only vancomycin, carbapenem, and colistin had resistance rates under 50%, the others were more than 50%, especially with the 3rd and 4th generation cephalosporins (66-83%), followed by aminoglycoside and quinolone (approximately 60%)[1]. Vancomycin and teicoplanin are glycopeptide antibiotics that are widely used in clinical practice in the treatment of infections caused by β-lactam-resistant Gram-positive bacteria. Beside their efficacy, they have been demonstrated to be associated with many adverse events, including thrombocytopenia. In 2014, vancomycin was 1 of 10 drugs that had the most frequently associated with drug-induced immune thrombocytopenia (DIIT) caused by drug-dependent antibodies (DDAbs)[2]. According to medical literature, teicoplanin also considered reducing platelets significantly with high dose (≥ 15 mg per kg per day)[3] but reversible or seldom at standard dose[4].

Although thrombocytopenia is a relatively rare adverse drug event, its consequences may be severe. It can lead to cerebral hemorrhage when platelet count under 20×10^9/L[5]. Therefore,

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it is important to extend our knowledge on this subject. The aims of this study were to determine the prevalence and related-factors for vancomycin or teicoplanin injection associated thrombocytopenia.

2. MATERIALS AND METHODS

2.1. Study settings

This descriptive cross-sectional study was conducted based on medical records at Thong Nhat hospital, Vietnam. The protocol of this study was approved by the Institutional Review Board of the Thong Nhat hospital (Project Number: 262 IRB/ QD- BVTN 26022015)

2.2. Inclusion criteria

- Patients aged 18 years and over.
- Patients admitted to the hospital from January 1st, 2013 to December 31st, 2014.
- Patients treated with vancomycin or teicoplanin injection for at least 48 hours.
- Patients with the baseline number platelets available in 5 days before therapy.
- Patients with platelet count examined at least 1 time during treatment with vancomycin or teicoplanin.

2.3. Exclusion criteria

- Patients using oral vancomycin.
- Patients with blood system disorders
- Patients with a reduction of platelet count associated with an original disease, including leukemia, myelodysplasia, aplastic anemia and tumors being treated using chemotherapy, splenomegaly, systemic lupus erythematosus.

2.4. Study process

Definition

In this study, thrombocytopenia was defined as a decrease in platelet count of at least 25% from baseline and lower than $100\times 10^9/L$[6]. Each platelet count during the treatment was compared with baseline. The reduction in platelet count was calculated as follows:

$$\text{Reduction} = \frac{((\textit{baseline platelet count-platelet count value on therapy})*100\%)}{(\textit{baseline platelet count})}$$

Patients had thrombocytopenia if value of at least 1 time during treatment course satisfied with the definition of thrombocytopenia. If more than one platelet value is available for a day, the lowest value was used.

Evaluation of the appropriateness of dosage

We judged the appropriateness of the dosage according to three literatures, including AHFS Drug Information Essentials 2011[7], Sanford guide to antimicrobial therapy 2013[3], and Vietnamese National Drug Formulary 2012[8]. The dosage was appropriate if satisfied one of the three literatures listed above.

2.5. Statistical analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) Program, version 20.0. Patient's data were presented as median (25^{th} – 75^{th} percentile) or percentage. The Mann-Whitney U test was used to compare means of continuous variables. Comparison rates of thrombocytopenia between the two groups of patients with vancomycin or teicoplanin were assessed using Chi-square. Time-to-event analysis was performed by computing Kaplan-Meier estimators (product-limit method) for each case of thrombocytopenia in this study. Survival distributions were compared using the log-rank test. Binary logistic regression analyses were performed to determine related factors of thrombocytopenia, with independent variables including age, gender, treatment at ICU, number of comorbidities, baseline serum creatinine, baseline eGFR, baseline platelet count, the appropriateness of dosage, and the concomitant use of thrombocytopenia-related drugs. The level of statistical significance was specified at $p < 0.05$.

3. RESULTS

3.1. Baseline characteristics of patients

In total 210 medical records were included in the study, 105 patients were treated with vancomycin and the others with teicoplanin. Median age of the study subjects was 79.5 (68.5-85) with a high proportion of male sex (60.0%).

Patients treated with teicoplanin were significantly older than those with vancomycin (median age 81 and 78, respectively, p=0.043). Moreover, patients in teicoplanin group more frequently treated at ICU, compared to those in vancomycin group (73.3% and 29.5%, respectively, p<0.001). Every patient in our study had at least one comorbidity. The two most common comorbidities were hypertension (59.5%) and respiratory failure (59.0%), followed by renal diseases, diabetes mellitus, and heart failure. The most popular indication for vancomycin and teicoplanin was pneumonia, including community and hospital acquired pneumonia, without a significant difference (80.0% and 89.5%, respectively, p=0.055). Vancomycin and teicoplanin were mainly used for MRSA infections. There were 4 cases infected with MSSA, including 2 cases of each group. The common dosage of vancomycin was 1.5-2 g per day and teicoplanin - 400 mg per day. The proportion of patients with appropriate dosing in vancomycin group was significantly higher than in teicoplanin group (86.7% and 65.7%, respectively, p <0.001). Patients' demographic and clinical characteristics were shown in Table 1.

Table 1. Patients' demographic and clinical characteristics

Characteristics	Vancomycin (n = 105)	Teicoplanin (n = 105)	p value
Age (years), median (25^{th} – 75^{th} percentile)	78 (66-84.5)	81 (74-86)	0.043
Gender, male, n (%)	64 (61)	62 (59.0)	0.778
Hospital ward of initiate therapy, n (%)			
ICU	31 (29.5)	77 (73.3)	<0.001
Non-ICU	74 (70.5)	28 (26.7)	
Number of comorbidities, median (25^{th} – 75^{th} percentile)	2 (1-2)	2 (1-3)	0.239
Comorbidities, n (%)			
Hypertension	66(62.9)	59(56.2)	0.325
Respiratory failure	34(32.4)	52(49.5)	0.012
Renal diseases	27(25.7)	29(27.6)	0.755
Diabetes mellitus	26(24.8)	26(24.8)	1.000
Heart failure	22(21.0)	27(25.7)	0.415
Diagnosis			
Pneumonia	84 (80.0)	94 (89.5)	0.055
Bacteremia	7 (6.7)	14 (13.3)	0.107
Skin and soft tissue infections	9 (8.6)	7 (6.7)	0.603
Others	9 (8.6)	2 (1.9)	0.030
Organisms			
MSSA	2 (1.9)	2 (1.9)	1.000
MRSA	45 (42.9)	47 (44.8)	0.781
Entercoccus spp.	6 (5.7)	6 (5.7)	1.000
Others Gram-positive	20 (19.0)	11 (10.5)	0.207
Baseline SCr, median (25^{th} – 75^{th} percentile) (25^{th}–75^{th} percentile) (μmol/L)	96 (66-133.5)	105 (67.5-169)	0.347
Baseline eGFR group (mL/min), n (%)			
< 60	48 (45.7)	67 (63.8)	0.008
≥ 60	57 (54.3)	38 (36.2)	
Duration of therapy, median (25^{th} – 75^{th} percentile)	13 (9-15)	13 (10-14)	0.388
The appropriateness of dosage			
Appropriate	91 (86.7)	69 (65.7)	<0.001
Inapropriate	14 (13.3)	36 (34.3)	

3.2. Thrombocytopenia

Prevalence

The baseline platelet count of the two groups was not significant difference (p = 0.101). Numbers of patients with thrombocytopenia in vancomycin group and teicoplanin group were 17 (16.2%) and 21 (21.9%), respectively, without a significant difference (p = 0.292).

Identifying adverse drug event - thrombocytopenia is important, but time-to-event is more important. Patients' platelet count started decreasing in the second day in both vancomycin and teicoplanin groups. The prevalence of thrombocytopenia in the two groups was not different significantly at any time-point, excepted for the 8th day of the therapy (p = 0.047). Kaplan-Meier plots of the probability of non-thrombocytopenic patients were displayed in figure 1. In addition, we compared the time-to-event of these outcomes. The result showed that survival distributions were similar between treatment groups (log-rank = 0.159).

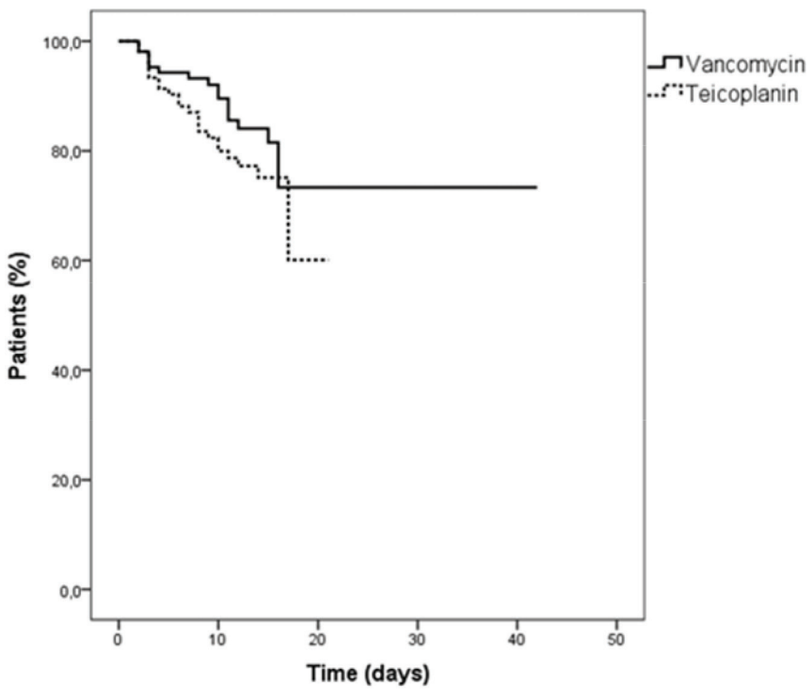

Figure 1. Kaplan-Meier plots of the probability of non-thrombocytopenic patients in the two treatment groups. Log-rank = 0.159

Related-factors

Related-factors for thrombocytopenia in vancomycin and teicoplanin groups were showed in table 2 and 3, respectively.

4. DISCUSSION

4.1. Baseline characteristics of patients

The median age of patients using vancomycin in our study was 78 (66-84.5), and was higher than those in Le Van Anh's study in 2013 at Bach Mai hospital, Vietnam[14], which was 52 (36-64). Meanwhile, the median age of patients using teicoplanin in our study was 81 (74-86), and was higher than those in a study of So-Yun Nah et al. in a Korean hospital in 2014[15], which was 65.9 (17-87). Those differences might be due to the characteristics of patients in Thong Nhat hospital who were mainly veterans, retirees, and old people.

The median age of patients using teicoplanin was statistically higher than those using vancomycin (p=0.043). This can be

Table 2. Related-factors for thrombocytopenia in vancomycin group

	OR	95% CI		p-value
		Lower limit	Upper limit	
Age	1.015	0.973	1.059	0.492
Baseline SCr	0.992	0.976	1.007	0.292
Number of comorbidities	0.947	0.514	1.746	0.861
Gender (male)	5.740	1.115	29.541	0.037
Hospital ward of initiate therapy (ICU)	1.460	0.419	5.085	0.553
eGFR (≥ 60 mL/min)	0.440	0.082	2.357	0.338
Baseline platelet count (≥ 142×10^9/L)	1.746	0.365	8.349	0.485
Concomitant use of thrombocytopenia-related drugs*(yes)	1.596	0.460	5.532	0.461
The appropriateness of dosage (appropriate)	0.140	0.031	0.628	0.010

**Thrombocytopenia-related drugs: unfractionated heparin, low molecular weight heparin, furosemide, spironolactone, β-lactam, ciprofloxacin, rifampicin, and sulfamethoxazole -trimethoprim*[2,17,18].

Table 3. Related-factors for thrombocytopenia in teicoplanin group

	OR	95% CI		p-value
		Lower limit	Upper limit	
Age	1.010	0.959	1.063	0.715
Baseline SCr	1.004	0.997	1.012	0.209
Number of comorbidities	0.812	0.482	1.370	0.436
Gender (male)	0.350	0.111	1.104	0.073
Hospital ward of initiate therapy (ICU)	5.054	1.077	23.719	0.040
eGFR (≥ 60 mL/min)	0.760	0.175	3.296	0.714
Baseline platelet count (≥ 142×109/L)	0.267	0.087	0.823	0.021
Concomitant use of thrombocytopenia-related drugs*(yes)	1.321	0.312	5.588	0.705
The appropriateness of dosage (appropriate)	0.599	0.159	2.261	0.450

** Thrombocytopenia-related drugs: unfractionated heparin, low molecular weight heparin, furosemide, spironolactone, β-lactam, ciprofloxacin, rifampicin, and sulfamethoxazole- trimethoprim*[2,17,18].

explained by the results of some studies, including Davey P.G study[10] in 1991, Wilson A.P.R study[4] in 1998, Svetisky S. study[11] in 2009, and Cavalcanti A.B. study[9] in 2010, which supposed that the efficacy of vancomycin and teicoplanin in clinical outcome and bactericidal effect was equivalent, but the summary prevalence of adverse drug events, nephrotoxicity, and pseudoallergy caused by teicoplanin was statistically lower, compared to vancomycin. In addition, the old group of patients frequently had a large number of risk factors for adverse drug reactions due to the decrease in function of organs. Therefore, the use of teicoplanin in the old group of patients might aim to limit those adverse reactions.

The prevalence of male in both groups of patients (vancomycin – 61.0% and teicoplanin – 59.0%) was higher than female. The difference in gender ratio between two groups was not statistically significant (p=0.778).

The ratio of sex in patients using vancomycin was similar to the result of Le Van Anh et al. study[14] at Bach Mai hospital in 2013 using descriptive cross-sectional method to analyze profiles of 256 patients (male accounted for 62.1%). In another study of Fraser T.F.[16] in 2005 among 296 outpatients using vancomycin, which is performed by a home health care center and an American hospital, recorded that male accounted for 62.5%. However, the equivalence in sex ratio was revealed in a study of Bollinger M.[17] in 2015 at a suburban hospital in Canada with 50.8% male. In study of So-Yun Nah[15] using retrospective analysis in patients treated with teicoplanin in a Korean hospital, male accounted for 59.0% (36/61). However, this proportion was 72.2% (146/202) in a retrospective analysis study of Pea F. et al. in 2013[18] among patients treated with teicoplanin. It might be due to characteristics of patients in Thong Nhat hospital, who was mainly veterans, which led to higher proportion of male, compared to female, in most recorded diseases.

The distribution of patients in different hospital wards, where vancomycin and teicoplanin were initiated for treatment, was statistically significant (p<0.001). Vancomycin was used significantly in non-ICU ward (70.5%). This was similar to the result of Le Van Anh study in 2013 about vancomycin use at Bach Mai hospital[14] with the prevalence of non-ICU being 78.5%. Patel N. study in 2011[19] at a veteran-care hospital in America also revealed similar result with 79.3% vancomycin used in non-ICU ward. In contrary, teicoplanin was used more frequently in ICU ward (73.3%), compared to vancomycin (29.5%) (p=0.000). Supposedly propensity of doctors in Thong Nhat hospital to prescribe teicoplanin was initiated for old patients in exhausted condition. According to medical literature, teicoplanin had equivalent efficacy, but more safety and less unwanted effects, compared to vancomycin[4,9,10,11].

Hypertension accounted for the largest proportion in both groups of patients (vancomycin – 62.9% and teicoplanin – 56.2%). This fit with the analyzing sample in our study because 93.3% patients were 55 years old and over, which were a risk factor for hypertension. According to information updated in 2013 of AHA (Statistical Fact Sheet 2013 Update) about hypertension, the prevalence of hypertension is in accord with the increase of age. From age of 55, prevalence of hypertension is over 50% in both sexes.

For the group of patients using vancomycin, similar result was also observed in study of Patel N. [19] in 2011 performed in a veteran-care hospital in America with 64.1% of patients diagnosed with hypertension. This prevalence was the highest among recorded comorbidities. In 2014, a study of Mueller K.[20] performed in patients treated with vancomycin in emergency ward also revealed that hypertension was the most popular comorbidity. Other diseases related to the elderly were also popular. Among those diseases, diabetes, heart failure, and renal diseases had no statistically different prevalence between two groups of patients (>20%).

Patients using teicoplanin had a statistically higher prevalence of respiratory failure than vancomycin group at 49.5% and 32.4%, respectively (p=0.012). This was due to 80.2% (69/86) of patients with respiratory failure treated in ICU ward. In addition, as mentioned above, teicoplanin was used significantly in this ward.

Pneumonia was the main indication of vancomycin (80.0%) and teicoplanin (89.5%) without statistical difference between two groups (p=0.055). Bacteremia was the second most popular indication (6.7% and 13.3%, respectively). Skin and soft tissue infections were the least popular indications (8.5% and 6.7%, respectively). Other diseases were treated more frequently with vancomycin, compared to teicoplanin (p=0.030).

Meanwhile, the prevalence of pneumonia indication in patients using vancomycin was only 10.5% (27/256) in the study of Le Van Anh at Bach Mai hospital, while the highest prevalence was the indication of skin and soft tissue infections – 21.9% (56/156)[14]. The main indication for pneumonia in our study might be due to the characteristics of patients in Thong Nhat hospital, including old age, multi-pathology, senility, and long period of hospitalization, which could easily led to pneumonia, especially hospital acquired pneumonia.

4.2. Thrombocytopenia

During treatment period with vancomycin and teicoplanin, patients' platelet count started decreasing in the second day in both groups. Depending on point in time that thrombocytopenia observed, its mechanism can be predicted as immune mechanism because of prolong start of non-immune mechanism, which needs a few weeks to deplete an enormous amount of megakaryocytes-producing platelet cells[21]. In 2014, vancomycin was mentioned in a list of 10 drugs causing thrombocytopenia via immune mechanism by drug-dependent antibodies, which were most recorded, according to study of Curtis B.R.[2]. However, there has not been a research that reveals thrombocytopenia mechanism of teicoplanin.

The difference of thrombocytopenia prevalence between two groups was not statistically significant, excepted for 8th day (p=0.047). The result of log-rank test (p = 0.159) showed that thrombocytopenia rates of two groups in accord with treatment time were not statistically significant.

Consequently, by using Chi-square χ^2 to analyze prevalence and Kaplan-Meiere estimator to analyze survivor function, it was demonstrated that the ability to cause thrombocytopenia and rate of thrombocytopenia of vancomycin and teicoplanin were equivalent with common dosage being 1-2g/day and 0.4g/day, respectively. The result showed that prevalence of thrombocytopenia in two groups was equivalent. In addition, 2 patients in group treated with vancomycin used enoxaparin and fondaparinux in the previous day before thrombocytopenia observed. Similarly, 2 patients treated with teicoplanin used heparin in the previous day before this adverse drug event observed. However, this did not increase significantly prevalence of thrombocytopenia in two groups of our study.

This result was similar to Wilson A.P.R.[4] study in 1998, the thrombocytopenia prevalence of teicoplanin with dosage at 6 mg/kg/day (about 0.4 g/day) was similar to 15mg/kg/day vancomycin (about 1g/12h). It was also observed that thrombocytopenia prevalence of teicoplanin with 12mg/kg/day and more (above 0.8g/day) was statistically higher, compared to vancomycin with 15mg/kg/12h (about 1g/12h). Teicoplanin can cause reversible thrombocytopenia only if its dose is higher than common dosage without relating to patient's clinical condition. According to Sanford guideline in 2013[3], it was also mentioned about serious thrombocytopenia of teicoplanin with dosage over 15mg/kg/day (about 1g/day).

For vancomycin-associated thrombocytopenia, related factor was sex (male) (OR 5.740; 95% CI 1.155-29.547; p = 0.037) and the appropriateness of drug dosing was a protective factor (OR 0.140; 95% CI 0.031-0.628; p = 0.010). For teicoplanin-associated thrombocytopenia, related factor was treatment in the ICU (OR 5.054; 95% CI 1.077-23.791; p = 0.040) and protective factor was baseline platelet count (≥ 142 x 10^9/L) (OR 0.267; 95% CI 0.087-0.823; p = 0.021).

We should mention several limitations of our study. This was a descriptive cross-sectional study based on medical records. Therefore, the collection of data was passive. The platelets were not examined everyday, the day that thrombocytopenia occurred in study was just the day that thrombocytopenia was found. Moreover, we could not determine the relationship between the trough concentrations of vancomycin or teicoplanin and adverse event thrombocytopenia. Despite these, this study provides useful data for future comparisons.

5. CONCLUSION

Thrombocytopenia was observed in 16.2% of patients received vancomycin and 21.9% of patients received teicoplanin (p = 0.292). For vancomycin-induced thrombocytopenia, related factor was sex (male) and the appropriateness of dosage was protective factor. For teicoplanin-induced thrombocytopenia, related factor was treatment at ICU department and protective factor was baseline platelet count (≥ 142×10^9/L). it is essential to perform dosing adjustment in patients used vancomycin, especially male, and frequently monitor the number of platelets in patients treated in ICU with low baseline platelet count when using teicoplanin to minimize the frequency of thrombocytopenia in patient during treatment course.

6. ACKNOWLEDGEMENTS

The authors thank TN Hospital for granting permission to access of medical

records. This study was financially supported by the Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam. We would like to thank Ms. Luu Thi Hoa and Mr. Ngo Van Tinh for editing the manuscript.

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