Saudi Pharmaceutical Journal 29 (2021) 616–624

Contents lists available at ScienceDirect

Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Original article

Causes of vancomycin dosing error; problem detection and practical solutions; a retrospective, single-center, cross-sectional study

Abdullah M. Alzahrani [a,b,c], Anjum Naeem [a,b,c], Ali F. Alwadie [a,b,c], Khalid Albogami [a,b,c], Rami M. Alzhrani [d], Samah S. Basudan [e], Yahya A. Alzahrani [a,f,*]

[a] King Abdullah International Medical Research Center, Jeddah, Saudi Arabia
[b] King Saud bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
[c] Pharmaceutical Care Department, Ministry of National Guard - Health Affairs, Jeddah, Saudi Arabia
[d] Department of Pharmaceutics and Industrial Pharmacy, College of Pharmacy, Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia
[e] Department of Pharmacy, King Abdullah Medical Complex, Ministry of Health, Jeddah, Saudi Arabia
[f] Department of Pharmacy, East Jeddah Hospital, Ministry of Health, Jeddah, Saudi Arabia

ARTICLE INFO

Article history:
Received 1 December 2020
Accepted 18 April 2021
Available online 6 May 2021

Keywords:
Vancomycin
Abnormal Trough
Sampling time
Weekend's effect
Duty time
Number of interventions

ABSTRACT

Vancomycindosing error and inappropriate monitoring is a common problem in hospital daily practice. In King Abdulaziz Medical City (KAMC) in Jeddah, a high percentage of abnormal vancomycin trough levels is still detected despite using the recommended dose. Therefore, the current research objective is to study the major causes of vancomycin dosing errors. This retrospective, single-center, cross-sectional study was carried out at KAMC hospital in Jeddah from January 1st until December 31st 2019. All adult patients (≥15 years) who received vancomycin and had an initial abnormal trough level at the measured steady-state were included in this study. 472 patients have met the study inclusion criteria.

The current study evaluated the factors that play a role in causing vancomycin trough level abnormalities such as sampling time, vancomycin dosing, and patient's pharmacokinetic and pharmacodynamic variations.

In this study, we found that pharmacokinetic and pharmacodynamic variability was attributed to 65% of vancomycin's abnormal trough level. Also, the result showed a significantly increased odds of the low trough in the non-elderly group (OR 6, 95% CI 2.48 – 14.9, P < 0.001) and febrile neutropenic patients (OR 2.21, 95% CI 1.119 – 4.365, P < 0.05). However, the odds of high trough levels were significantly elevated among patients who have CrCl < 50 ml/min (OR 5, 95% CI 1.262–20.539, P < 0.05). In addition, the present investigation revealed that the occurrence of abnormal vancomycin levels was not affected by daily duty time or working days (p > 0.05). The current study indicated that vancomycin dosing errors were common in KAMC patients; thus, there is an unmet need to evaluate the causes of vancomycin abnormal trough level and optimize a strategy that would enhance the therapeutic effectiveness and minimize the potential toxicity.

1. Introduction

Vancomycin is one of the old antibiotics used in treating infected patients with methicillin-resistant staphylococcus aureus (MRSA). One of the major reasons for vancomycin resistance is using a universal empirical dose (1 g every 12 h) in all patients regardless of their weight, creatinine clearance, or conditions. The universal empirical dose may lead to a sub-therapeutic level < 10 μg/ml in patients with a weight ≥ of 80 kg and normal renal function i.e. ≥ 90 ml/min (Devabhakthuni et al., 2012). Therefore, using a personalized vancomycin dose is essential to minimize the toxicity that arises from pharmacokinetics variability. Differences in pharmacokinetics might be attributed to certain conditions such as neutropenia, intensive care units (ICU), and body burns (Al-Kofide et al., 2010). In neutropenic and obese patients, studies revealed that the volume of distribution and

* Corresponding author.
E-mail address: yalzahrani5@moh.gov.sa (Y.A. Alzahrani).
Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.jsps.2021.04.023
1319-0164/

clearance of neutropenic patients is high; thus, a higher dose is required to compensate the vancomycin decreased level (Hochart et al., 2011; Guilhaumou et al., 2016; Bury et al., 2019). Moreover, the obese vancomycin dose is calculated based on the actual body weight; however, in some patients with a short half-life, they may require increasing dosing frequency (Vance-Bryan et al., 1993; Bauer et al., 1998). Furthermore, many physiological variations occurred in elderly patients play a role in increasing the volume of distribution and decreasing creatinine clearance, making them vulnerable to toxicity more than adult and young patients (Sánchez et al., 2010; Barber et al., 2016).

Despite the use of vancomycin since the middle of 1950, the optimal dosing strategy remained controversial, and the dosing practice differs from one institution to another (Jarkowski et al., 2012). Koppula et al., 2015 reported that the patients' high trough level is attributed to wrong sampling time (21%), improper dosing (19%), changes in renal function (23%), and pharmacokinetics pharmacodynamics variability (36%). Another factor that has to be considered in all patients is the individual biological variation, such as the volume of distribution, protein binding, and drug clearance, that affect vancomycin dosing (Koppula et al., 2015). (Kabbara et al., 2018) revealed that only 15.7% of the patients were within the target therapeutic level; while, 69% of the patients had improper vancomycin monitoring (Kabbara et al., 2018). Based on the above-mentioned causes of the vancomycin dosing errors, there is an unmet need to create a strategy to improve the accuracy of vancomycin dosing and minimize the potential toxicity.

The current single-centered study was conducted in KAMC - Jeddah to identifying the associated causes of vancomycin abnormal trough level and improve the overall vancomycin dosing accuracy. Knowing the causes will facilitate creating a strategy to minimize the dosing error and the overall vancomycin toxicity.

2. Materials and methods

2.1. Place of study

The current work was carried out at KAMC hospital in Jeddah in 2019.

2.2. Study Design, Setting, and patient population

This retrospective, single-center, cross-sectional study was approved by the institutional review board at King Abdullah International Medical Research Center (KAIMRC) (RJ/20/026/J). The Data collection was conducted in the period from January 1st until December 31st, 2019 by using a data collecting sheet evaluated by two expert clinical pharmacists in the field, the data was derived from the electronic reporting and recording system. All eligible patients in that period were reviewed. The initial vancomycin trough levels, which were greater than 20 μg/ml or below 10 μg/ml, were evaluated to determine the abnormal levels' causes. Patients were divided into three groups based on the first steady-state trough level: low, normal, and high groups.

2.3. Vancomycin dosing and monitoring

Based on the current clinical practice at KAMC - Jeddah, the initial vancomycin dose is 15–20 mg/kg every 12–8 h using the actual body weight and administered over 90 to120 min. Serum trough is usually done as a routine for all patients with normal kidney function 30 min before the 4th dose (Murphy et al., 2006; Adane et al., 2015). The subsequent doses were adjusted according to the trough level.

2.4. Inclusion and exclusion criteria

All adult patients (≥15 years) who received vancomycin and had an initial abnormal trough level measured at a steady-state were included in this study. We excluded ICUs, hemodialysis, burned, and pediatric patients. Abnormal trough level was defined as a sub-therapeutic level (<10 μg/ml) or supra-therapeutic level (>20 μg/ml) measured at a steady state. Steady-state was defined as a "serum sample drawn 30 min to 1 h before the fourth scheduled vancomycin dose". The causes of abnormal trough levels were classified into four categories: trough level checked at the wrong time, improper dosing, pharmacokinetic and pharmacodynamic (PK/PD) variability, and others. The PK/PD variability was included (age, BMI, CrCl, and neutropenia). The patients who did not meet the study criteria to categorize for one of the three categories of abnormal trough causes during the data collection were classified as others.

2.5. Patient groups

To examine the effect of each PK variable on the abnormal trough level, our patients were divided based on age, BMI, CrCl, and neutropenia into two groups for each variable; elderly (≥65 years) and non-elderly groups (<65 years), obese (≥30 kg/m^2) and non-obese patients (<30 kg/m^2), patients with CrCL ≥ 50 ml/min (receive a full dose every 12 h), while patients with CrCL < 50 ml/min required dose adjustment. Moreover, patients were categorized based on neutropenia occurrence into; neutropenic patients "absolute neutrophil count (ANC) < 1.5 cells/nL " and non-neutropenic patients "the absence of neutropenia was defined as ANC ≥ 1.5 cells/nL, or in case no differential of the WBC was available, a normal WBC value defined as WBC > 4 cells/nL plus no clinical suspicion of neutropenia" (Bury et al., 2019).

2.6. Endpoints

2.6.1. Primary endpoints

To find the prevalence and causes of vancomycin dosing error that leads to sub-therapeutic level (<10 μg/ml) or supra-therapeutic level (>20 μg/ml) in adult non-ICU patients at KAMC hospital.

2.6.2. Secondary endpoints:

- To assess the appropriateness of interventions performed to achieve the optimal vancomycin trough concentration.

Appropriate intervention is defined as the dose modification by the physician or clinical pharmacist after detection of abnormal trough level, which leads to obtaining the target level. Otherwise, it will be considered inappropriate.

- To determine the impact of the time of vancomycin initiation on the likelihood of abnormal trough serum vancomycin concentrations.
- To investigate the effect of working during weekdays or weekends on the occurrence of abnormal trough serum vancomycin concentrations.

In KAMC - Jeddah, inpatient services are covered 24 h, seven days per week. KAMC - Jeddah used a three-shift system (morning, afternoon, and night) with eight hours of duty. The clinical pharmacist duty only during business hours from 0800 to 1700 from Sunday to Thursday. There is no clinical pharmacist coverage after business hours, and during weekends, all clinical responsibilities during this time are covered by a senior expert pharmacist.

- To determine the number (s) of interventions required to reach the target vancomycin level.

2.7. Statistical analysis

All data were analyzed using a statistical package for the social sciences (SPSS) version 26.0 (SPSS Inc, Chicago, IL, USA). The Kolmogorov-Smirnov test and histogram were used to determine the distribution of the data. Demographics were expressed as frequencies and percentages for categorical variables and continuous variables were presented as mean ± SD or median (interquartile range) where applicable. The comparisons between the two groups were performed using contingency table analysis with a χ^2 test or Fisher exact test and Mann-Whitney U tests for categorical variables. The Kruskal Wallis test was used to compare three or more groups for categorical variables. The crude odds ratio with a 95% confidence interval (95% CI) of abnormal trough level was calculated among each PK variables (age, BMI, CrCl, and neutropenia) and different hospital units (medical, oncology, surgical, and ER). The significant PK variable association found in χ^2 test was included in multivariate logistic regression analysis. Multivariate logistic regression analysis was performed to identify independent predictors of abnormal trough level using age, BMI, CrCl, and neutropenia as potential predictor variables. The adjusted odds ratio with 95% IC in the multivariate logistic regression model was also calculated. All reported P values were 2-sided, P-value of <0.05 was considered statistically significant.

3. Result

Out of the 1497 patients who received vancomycin, 472 patients were met the study inclusion criteria and effectively analyzed, while 1025 were excluded (Fig. 1). The majority of the enrolled patients were in the oncology unit (n = 195, 41.2%) and medical area (n = 117, 24.7%). The mean vancomycin dose was 1884 mg/day and SD of ± 586 mg. The patient's BMI was ranged from normal (31.9%) to underweight (11.2%) and class III obesity (5.9%). 46.5% of the patients were adults, whereas the young adult and elderly were 16.3% and 37.2%, respectively. Men and women were distributed equally in this study. Among the 472 trough concentrations, 204 (43.6%) were lower than 10 μg/ml while 80 (16.9%) were higher than 20 μg/ml (Table 1).

3.1. Prevalence and causes of vancomycin abnormal level

Sixty-five percent of the abnormal vancomycin trough level was due to the PK/PD variability. The improper dose was responsible

Table 1
Demographic characteristics of the study patients.

Variable	Frequency	(%)
Age (yrs)		
Young Adult (≤30)	77	16.3
Adult (>30 - <65)	220	46.5
Elderly (≥65)	176	37.2
BMI (kg/m^2)		
Underweight (≤18.5)	53	11.2
Normal (18.5–24.9)	151	31.9
Overweight (25.0–29.9)	140	29.6
Class I obesity (30.0–34.9)	66	14.0
Class II obesity (35.0–39.9)	35	7.4
Class III obesity (≥40)	28	5.9
CrCl (ml/min)		
>90	206	43.6
50–90	187	39.5
15–50	77	16.3
<15	3	0.6
Gender		
Male	247	52.2
Female	226	47.8
Trough (μg/ml)		
Low (≤10)	204	43.6
Normal (10–20)	188	39.7
High (≥20)	80	16.9

BMI = Body Mass Index, CrCl = Creatinine Clearance.

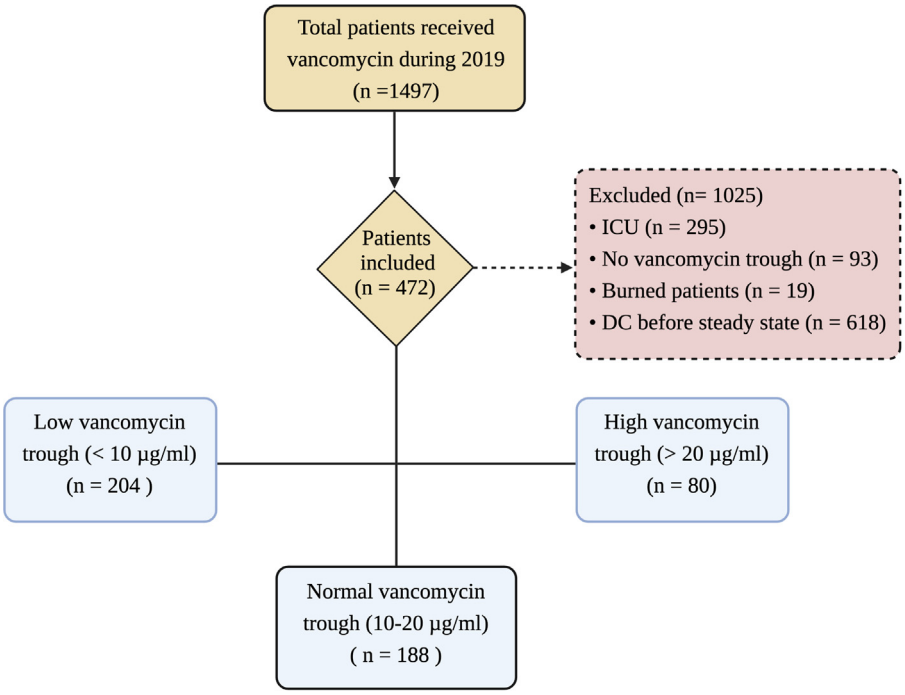

Fig. 1. Flow diagram for the inclusion of study patients.

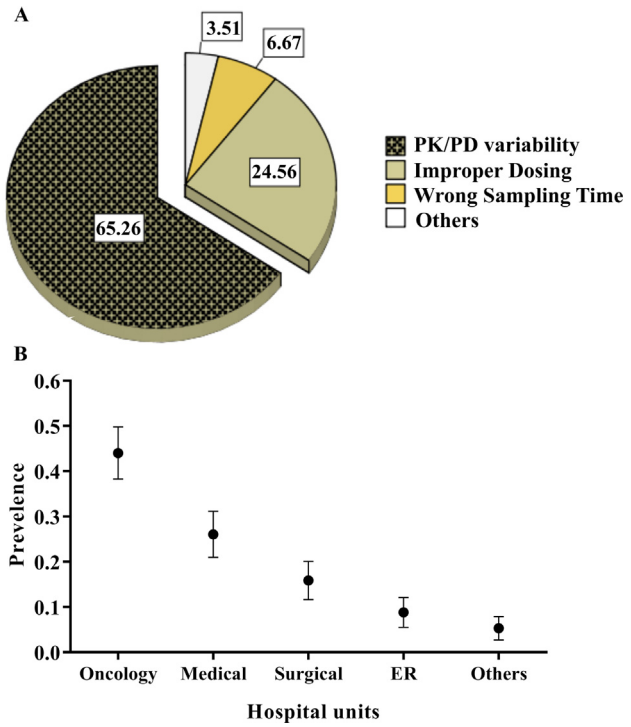

Fig. 2. **(A)** Prevalence of identified causes for abnormal vancomycin trough levels. **(B)** The proportion and the 95% confidence interval (CI) of abnormal Vancomycin trough concentrations observed in different hospital units. n = 284.

for 24.56% of the total abnormal trough level causes and 6.67% of all cases were due to the obtaining of the specimen at the wrong time (Fig. 2**A**). 44% of abnormal trough level was in the oncology unit, and 24% in the medical unit while surgical and emergency department representing 16% and 8% of the total events (Fig. 2**B**).

Interestingly, there is an increased odds of low trough levels among non-elderly patients (OR = 5.56, CI 95% = 3.5–8.7, P < 0.001) compared to an elderly patient. Moreover, the low trough's odds are increased in patients with high CrCl (CrCl ≥ 50 ml/min) (OR = 3.55, CI 95%: 1.87 to 6.6, P < 0.001) compared to the low CrCl group (CrCl < 50). Also, subgroup analyses were performed based on units, and the results showed that a significantly increased odds of the low trough in medical unit patients with CrCl ≥ 50 ml/min (OR = 6.192, 95% CI = 2.084 to 16.39, P < 0.001) compared with medical unit patients have CrCl < 50 ml/min. Similarly, the results demonstrated a significant increase in odds of high troughs among oncology patients those with CrCl < 50 ml/min (OR = 5.022, 95% CI = 1.362 to 16.15, P < 0.05) as compared with patients with CrCl ≥ 50 ml/min (Fig. 3**A).** Furthermore, it has been noticed that the oncology patients with febrile neutropenia were associated with lower trough vancomycin levels compared with the non-neutropenic group (OR = 2.424, 95% CI = 1.293 to 4.526, P < 0.01) and the median trough of the neutropenic group was 8, which corresponded to the sub-therapeutic range, whereas the non-neutropenic patient 13 (P < 0.0001) (Fig. 3**A)** and (Fig. 4**)**. After controlling all covariates, the multivariable logistic regression analysis showed that age, renal function, and febrile neutropenia were markedly associated with abnormal vancomycin trough levels. (Fig. 3**B)** illustrated a significantly increased odds of low trough in; the non-elderly group (OR 6, 95% CI 2.48 – 14.9, P < 0.001), febrile neutropenic patients (OR 2.21, 95% CI 1.119–4.365, P < 0.05) compared to the elderly and non-neutropenic groups respectively while the odds of high trough levels was significantly higher among CrCl < 50 ml/min patients (OR 5, 95% CI 1.262–20.539, P < 0.05) compared with patients have CrCl ≥ 50 ml/min. Also, the other variable in the model was not associated with increased or decreased the odds of abnormal trough comparing with the normal trough.

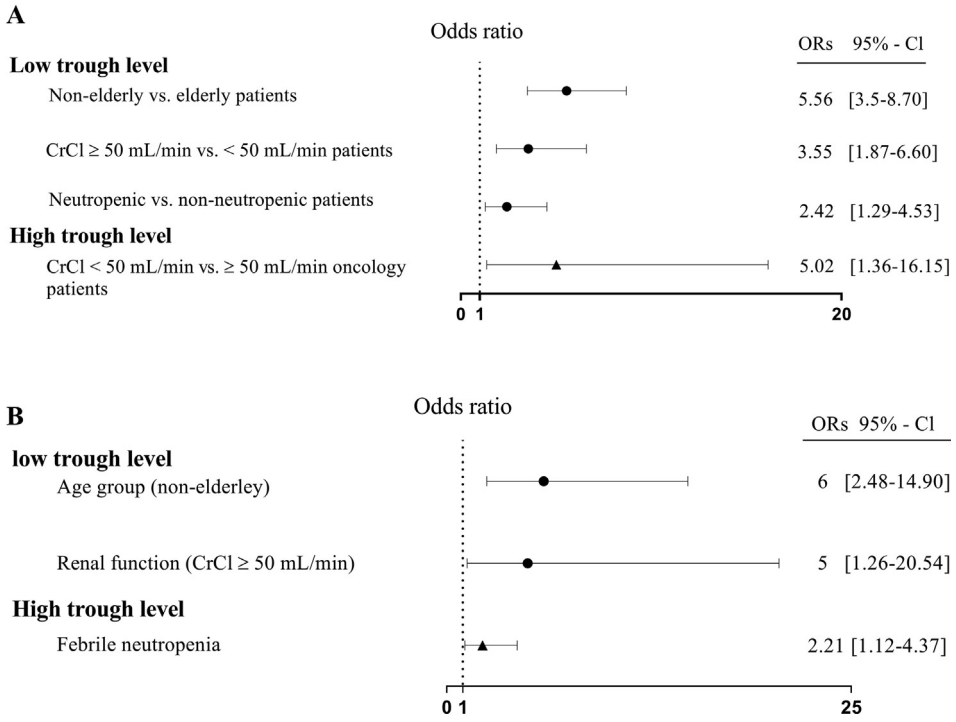

Fig. 3. The association between abnormal trough levels and various variables. (A) odds ratio. (B) Adjusted odds ratio.

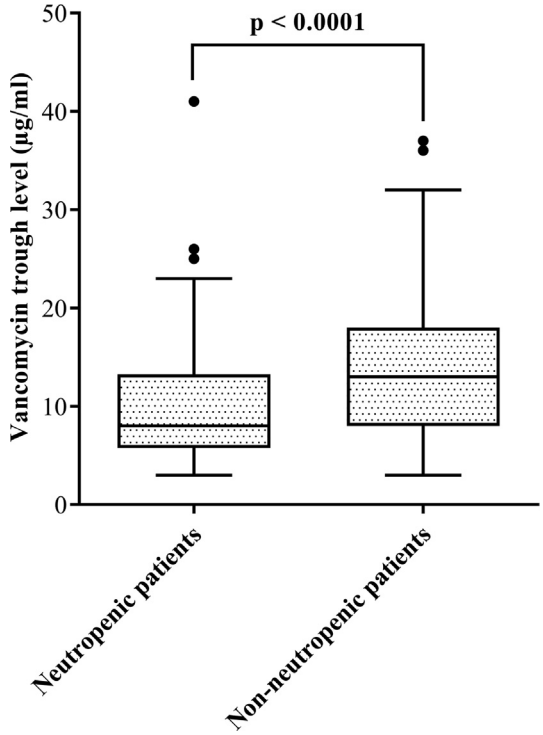

Fig. 4. Box plot showing significant differences in trough serum vancomycin concentrations between patients with and without neutropenia (p < 0.0001). Middle line: median; upper/lower box: upper or lower 25% of data; upper/lower bar: greatest or least value excluding outliers; dots: outliers (greater or lesser than 1.5 times of upper quartile).

3.2. The appropriateness of interventions performed to achieve optimal vancomycin trough concentration

One hundred ninety-two interventions were evaluated and the result showed that there is no significant difference among groups in terms of the appropriateness of interventions U = (Low = 144, High = 48) = 3384, z= – 0.254, P > 0.05. Depending on different hospital units, interventions were also assessed, and the result demonstrated that there is no statistical difference between low and high trough groups in all units χ^2 (4, n = 192) = 1.608 value, P > 0.05 (Fig. 5).

3.3. Impact of the time of vancomycin initiation on the likelihood of abnormal trough serum vancomycin concentrations.

Four hundred seventy-two trough values were evaluated. The summary of the distribution of trough between three different shifts illustrated in (Fig. 6**A).** A Kruskal-Wallis H test was conducted to examine the differences in trough groups (low, normal, high) across the duties time of initiation of the vancomycin dose during different shifts. The results showed no statistically significant difference in trough level groups between the different shifts, $\chi^2(2) = 1.117$, P > 0.05, with a mean rank 241.1 for the morning shift, 232.96 for the evening shift, and 224.14 for the night shift.

3.4. Effect of working during weekdays or weekend on the occurrence of abnormal trough serum vancomycin concentrations

A Kruskal-Wallis H test was conducted to examine the differences in distributions of trough groups across the working days of initiation of vancomycin and the result showed there is non-statistical significance on the distribution of trough groups between weekdays and weekend, ($\chi^2 = 1.067$, P > 0.05, df = 1), with a mean rank 233.22 for the weekdays and 247.42 for the weekend. (Fig. 6**B)** illustrated the distribution of normal and abnormal vancomycin trough concentrations cross working days.

3.5. Number of interventions required to reach the target vancomycin level

A total of 214 interventions were taken to reach the target level. The low-level group had higher proportions of patients who

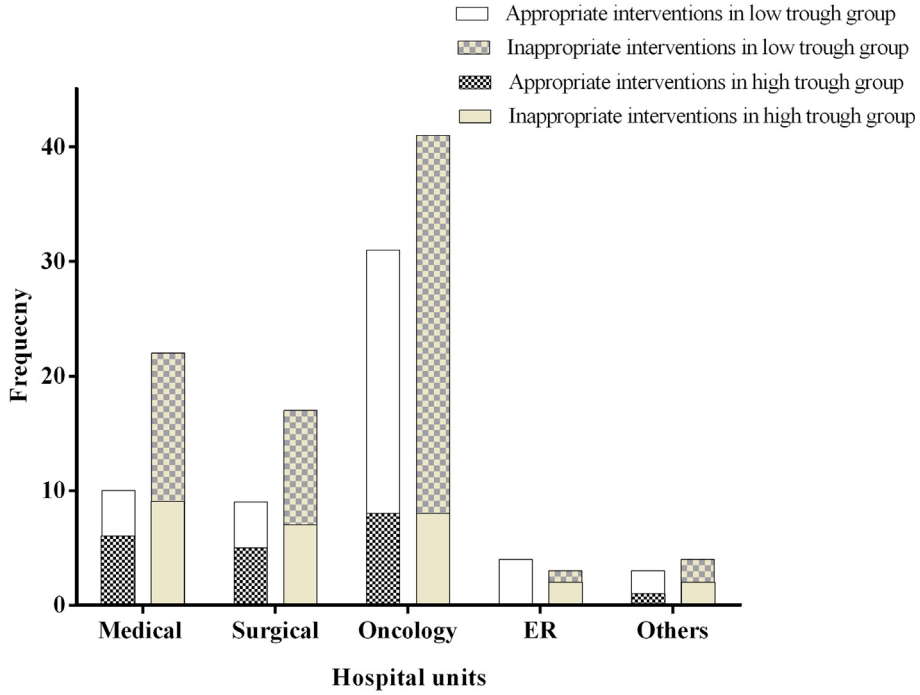

Fig. 5. Distribution of interventions were taken to achieve the optimal vancomycin trough Concentration between low and high trough groups in different hospital units.

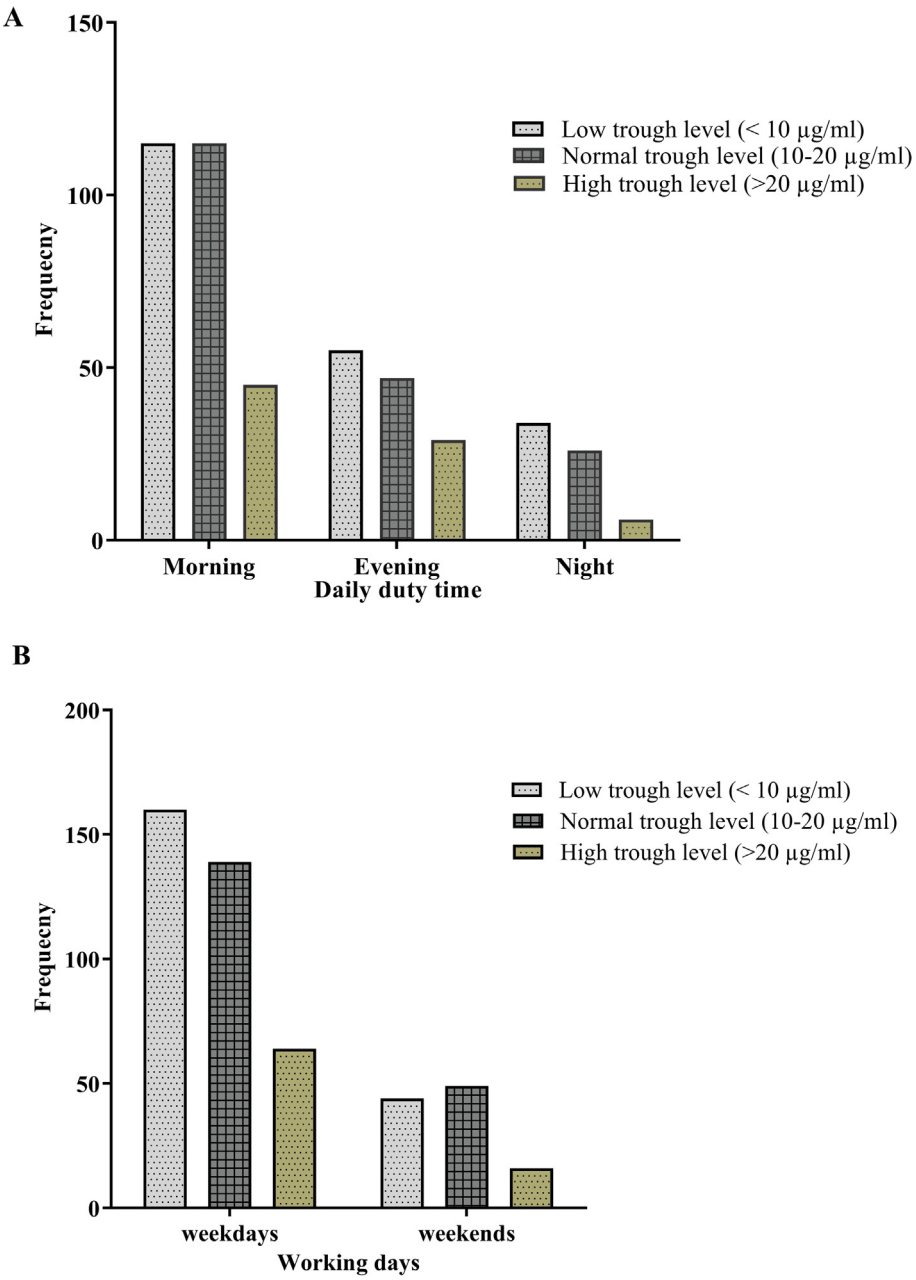

Fig. 6. **(A)** Distribution of normal and abnormal vancomycin trough concentrations cross daily duty time. **(B)** Distribution of normal and abnormal vancomycin trough concentrations cross working days.

required intervention more than the high-level group, 74.6%, and 25.4%. The most common source of errors associated with an increased number of the intervention was PK/PD variability > 40% for both groups. PK/PD variability was included (age, BMI, CrCl, and neutropenia). The result demonstrated that the oncology units account for the highest number of patients who required one intervention (Fig. 7.) Moreover, the result showed that the vast majority of the non-elderly patient with CrCl > 50 ml/min required one intervention as showed in (Table 2).

4. Discussion

The current study concluded that using a universal empirical dose of vancomycin (1 g every 12 hrs) is one of the reasons that cause receiving a sub-optimal dose in King Abdulaziz Medical City's patients. The data revealed that the sub-therapeutic initial trough concentrations of vancomycin were 43%. Interestingly, the improper sampling time led to 6.6% of the total error which consider low compared to other studies(Kabbara et al., 2018) (Melanson et al., 2013). We also found that neutropenic patients are associated with high odds of low trough compared with non-neutropenic patients OR = 2.4, P < 0.001. In agreement with this finding, Choi et al. found a strong association between low vancomycin trough level and neutropenia (Choi et al., 2017). The present investigation revealed that the distribution of abnormal vancomycin levels were not affected by weekends or weekdays shift. Thus, the abnormal vancomycin level was not associated with the weekend effect (P > 0.05). Moreover, we observed no difference in abnormal level rates during evenings and nighttime compared with the morning shift.

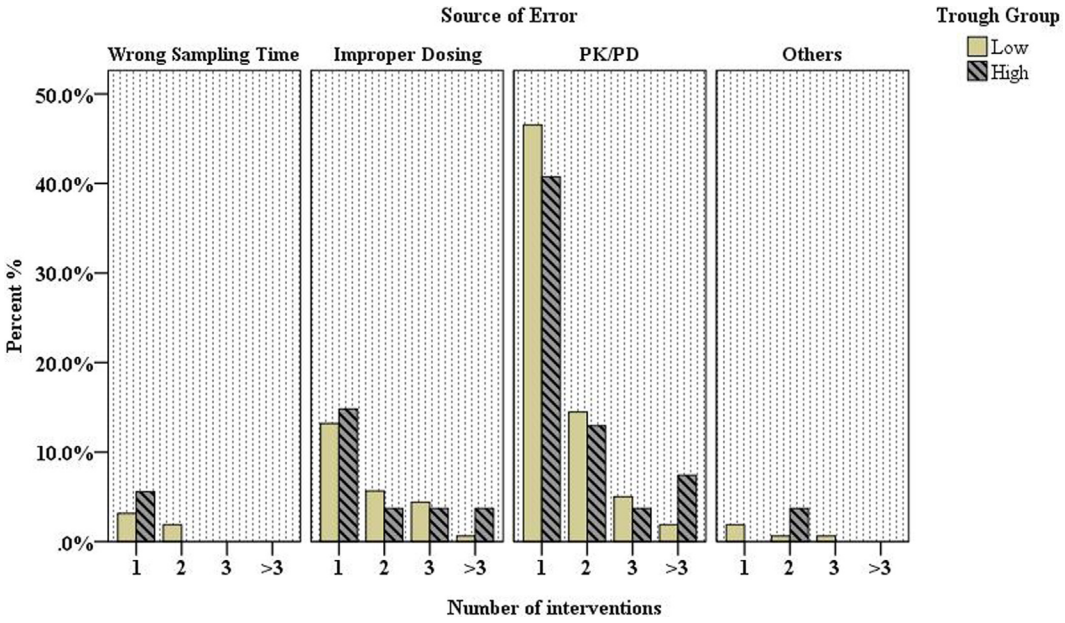

Fig. 7. The percentage of interventions required to reach the target vancomycin level among patients with low and high trough levels based on the source of vancomycin dosing error.

Table 2
The percentage of interventions required to reach the target vancomycin level among patients with CrCl < 50 ml/min and CrCl ≥ 50 ml/min based on the age group.

Age group	Number of interventions				
		1	2	3	>3
Elderly n (%)	CrCl < 50 ml/min	11(5.1)	4(1.9)	1(0.46)	3(1.4)
	CrCl ≥ 50 ml/min	22(10.2)	9(4.2)	3(1.4)	2(0.93)
Non- elderly n (%)	CrCl < 50 ml/min	4(1.9)	2(0.9)	–	–
	CrCl ≥ 50 ml/min	100(46.7)	32(14.9)	16(7.5)	5(2.33)
Total		137	47	20	10

Other studies have reported that administering of 1 g vancomycin to 92% of the ER department patients led to underdosing in 78% of those patients(Fuller et al., 2013). Thus, weight-based dosing is recommended to overcome the vancomycin sub-therapeutic level (Patanwala et al., 2009; Rybak et al., 2009). The cause of using an empirical fixed dose of vancomycin might be attributed to several reasons, such as lack of knowledge and fear of nephrotoxicity (Fuller et al., 2013; Al-Dorzi et al., 2019). The odds ratio of low trough among adult patients < 65 years is 5.5 folds higher than elderly patients > 65 years. The low trough level among adult patients is attributed to the rapid elimination process of vancomycin; thus, an increase in the dose frequency is suggested to be every 8 hr (Legal and Wan, 2010). Increasing the dose frequency (every 8 hr) helps in achieving the goal therapeutic concentration (13–22 μg/ml) in patients with CrCl > 70 ml/min (Kullar et al., 2011). On the other hand, the new vancomycin guideline-recommended a dose of 15 mg every 12 to 8 hr for all patients with normal kidney function. However, there are no specific criteria for who should start on twice or thrice daily dose (Rybak et al., 2020). Indeed the standardization of the vancomycin dose and using the same initial dose for all patients i.e., 15 mg/kg every 12 hr might be the cause of 46% of the adult patient with CrCl ≥ 50 ml/min required one intervention. Intervention which is easy to avoid and easy to correct by applying direct and straightforward pharmacokinetics calculation.

Inappropriate sampling time is another factor that impacts the vancomycin trough negatively. Kabbara et al. conducted a study in a tertiary hospital in Lebanon, and the results have shown that two-thirds of the patients had inappropriate sampling time (Kabbara et al., 2018). Kabbara et al. attributed the Inappropriate sampling time to several factors such as insufficient monitoring of renal failure patients. Melanson et al. performed and assessed educational, informational technology-based intervention for the nurses to reduce the vancomycin sampling error. The errors decreased from 39% to 32% which is not significant. The author summarized the reasons for that to unclear order by the prescriber and lack of effective communication between healthcare providers (Melanson et al., 2013). On the contrary, our results showed that the wrong sampling time led to 6.6% of the total errors. This percentage is considered low compared to the other studies (Melanson et al., 2013; Kabbara et al., 2018). This can be attributed to high adherence to the KAMC guideline and the wide expansion in clinical pharmacist services, which positively impacts the reduction of sampling time error and increasing commitment to the policy.

Regarding neutropenic patients, other studies found a strong association between low vancomycin trough level and neutropenia (Choi et al., 2017) which is comparable with our finding. A systemic review conducted in 2020 by He et al. confirmed that the current conventional vancomycin protocol is accompanied by a

low sub-therapeutics trough in patients with hematological malignancy or neutropenia. The mechanism by which neutropenia induces the sub-therapeutic level is not well understood (He et al., 2020); However, other studies explained this sub-therapeutic level due to the high volume of distribution and clearance in a neutropenic patient (Hochart et al., 2011; Guilhaumou et al., 2016). Neutropenia can cause the augmentation of vancomycin clearance, and many hypotheses exist to explain that, including; i) kidney function and urine output can be altered by cancer and excessive hydration, ii) induction of non-renal metabolism of vancomycin such as hepatic elimination by conjugation, and iii) vascular permeability is enhanced by infection and neutropenia, which leads to extravasations of vancomycin and caused decreased serum concentration (Al-Kofide et al., 2010; Choi et al., 2017).

The present investigation found no effect of weekends, weekdays, nighttime, or morning time on the distribution of abnormal vancomycin levels. This result is inconsistent with published studies that evaluate this effect on specific disease states. Miller et al. reported an increase in medication error rate during the evening and nighttime shifts relative to day shift and weekends relative to weekdays at academic, tertiary care children's hospitals (Miller et al., 2010). This variation can be explained by a gap of pharmacokinetic knowledge and wrong practice among all prescribers. Furthermore, understanding vancomycin pharmacokinetics and individualized the initial dose will enhance and decrease the abnormal level in a specific populations.

5. Conclusion

The present study showed that the underdosing of vancomycin in our hospital is predominant. Using universal dose in all patients was one of the leading causes of the vancomycin therapeutic level. Furthermore, age, renal function, and febrile neutropenia were markedly associated with abnormal vancomycin trough levels. The patient's pharmacokinetic and pharmacodynamic variations were another player that causes vancomycin trough level abnormality. Therefore, Personalized dosing would be one of the potential tools to minimize vancomycin toxicity. Also, evaluating the causes of vancomycin abnormal trough level and optimizing a strategy that would enhance the therapeutic effectiveness and reduce the potential toxicity is needed in our hospital.

6. Limitations

The study is retrospective in nature, which was done in one tertiary care center, limiting the ability to generalize the results. Our study was conducted in approximately medically stable patients, so such a result should not be extrapolated out of this range. Additionally, we evaluated only the initial trough resulting from empiric or therapeutic vancomycin dosing, and we did not evaluate clinical endpoints, such as microbiological cure or emergence of resistance. Finally, data collection was done through the institution's computerized system; consequently, no interventions were done on the hospital wards. Such studies enable you only to determine the association between vancomycin trough and various variables while the causality cannot be determined.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to express my very great appreciation to Dr. Ahmed Shaker for his valuable and constructive suggestions during the planning and development of this research work. His willingness to give his time so generously has been very much appreciated. Rami M. Alzhrani would like to acknowledge Taif University Researchers Supporting Project Number (TURSP-2020/209), Taif University, Taif, Saudi Arabia

References

Adane, E.D., Herald, M., Koura, F., 2015. Pharmacokinetics of vancomycin in extremely obese patients with suspected or confirmed Staphylococcus aureus infections. Pharmacotherapy. 35, 127–139.
Al-Dorzi, H.M., Eissa, A.T., Khan, R.M., Harbi, S.A.Al, Aldabbagh, T., Arabi, Y.M., 2019. Dosing errors of empirical antibiotics in critically ill patients with severe sepsis or septic shock: A prospective observational study. Int. J. Health Sci. 13, 48–55.
Al-Kofide, H., Zaghloul, I., Al-Naim, L., 2010. Pharmacokinetics of vancomycin in adult cancer patients. J. Oncol. Pharm. Practice. 16, 245–250.
Barber, K.E., Bell, A.M., Stover, K.R., Wagner, J.L., 2016. Intravenous Vancomycin Dosing in the Elderly: A Focus on Clinical Issues and Practical Application. Drugs Aging 33, 845–854.
Bauer, L.A., Black, D.J., Lill, J.S., 1998. Vancomycin dosing in morbidly obese patients. Eur. J. Clin. Pharmacol. 54, 621–625.
Bury, D., ter Heine, R., van de Garde, E.M.W., Nijziel, M.R., Grouls, R.J., Deenen, M.J., 2019. The effect of neutropenia on the clinical pharmacokinetics of vancomycin in adults. Eur. J. Clin. Pharmacol., 921–928
Choi, M.H., Choe, Y.H., Lee, S.G., Jeong, S.H., Kim, J.H., 2017. Neutropenia is independently associated with sub-therapeutic serum concentration of vancomycin. Clin. Chim. Acta 465, 106–111.
Devabhakthuni, S., Gonzales, J.P., Tata, A.L., Lee, S., Shah, P., Offurum, A.I., Gulati, M., 2012. Evaluation of vancomycin dosing and monitoring in adult medicine patients. Hospital Pharmacy. 47, 451–459.
Fuller, B.M., Mohr, N., Skrupky, L., Mueller, K., McCammon, C., 2013. Emergency department vancomycin use: Dosing practices and associated outcomes. J. Emerg. Med. 44, 910–918.
Guilhaumou, R., Marsot, A., Dupouey, J., Galambrun, C., Boulamery, A., Coze, C., Simon, N., André, N., 2016. Pediatric Patients with Solid or Hematological Tumor Disease: Vancomycin Population Pharmacokinetics and Dosage Optimization. Ther. Drug Monit. 38, 559–566.
He, N., Dong, F., Liu, W., Zhai, S., 2020. A systematic review of vancomycin dosing in patients with hematologic malignancies or neutropenia. Infection and Drug Resistance 13, 1807–1821.
Hochart, C., Berthon, C., Corm, S., Gay, J., Cliquennois, M., Tricot, S., Alfandari, S., 2011. Vancomycin serum concentration during febrile neutropenia in patients with acute myeloid leukemia. Medecine et Maladies Infectieuses. 41, 652–656.
Jarkowski, A., Forrest, A., Sweeney, R.P., Tan, W., Segal, B.H., Almyroudis, N., Wang, E. S., Wetzler, M., 2012. Characterization of vancomycin pharmacokinetics in the adult acute myeloid leukemia population. J. Oncol. Pharm. Practice 18, 91–96.
Vance-Bryan, K., Guay, D.R., Gilliland, S.S., Rodvold, K.A., Rotschafer, J.C., 1993. Effect of obesity on vancomycin pharmacokinetic parameters as determined by using a Bayesian forecasting technique. Antimicrobial Agents and Chemotherapy. 37, 436–440.
Kabbara, W.K., El-Khoury, G., Chamas, N.R., 2018. Prospective evaluation of vancomycin therapeutic usage and trough levels monitoring. J. Infection in Developing Countries 12, 978–984.
Koppula, S., Ruben, S., Bangash, F., Szerlip, H.M., 2015. Pitfalls in dosing vancomycin. Am. J. Med. Sci.
Kullar, R., Leonard, S.N., Davis, S.L., Delgado, G., Pogue, J.M., Wahby, K.A., Falcione, B., Rybak, M.J., 2011. Validation of the effectiveness of a vancomycin nomogram in achieving target trough concentrations of 15–20 mg/L suggested by the vancomycin consensus guidelines. Pharmacotherapy. 31, 441–448.
Legal, M., Wan, M., 2010. Influence of age on frequency of vancomycin dosing. Canadian J. Hospital Pharm. 63, 13–19.
Melanson, S.E.F., Mijailovic, S., Wright, A.P.M., Szumita, P.M., Bates, D.W., Tanasijevic, M.J., 2013. An intervention to improve the timing of vancomycin levels. Am. J. Clin. Pathol.
Miller, A.D., Piro, C.C., Rudisill, C.N., Bookstaver, P.B., Bair, J.D., Bennett, C.L., 2010. Nighttime and weekend medication error rates in an inpatient pediatric population. Ann. Pharmacother. 44, 1739–1746.
Murphy, J.E., Gillespie, D.E., Bateman, C.V., 2006. Predictability of vancomycin trough concentrations using seven approaches for estimating pharmacokinetic parameters. Am. J. Health-Syst. Pharm. 63, 2365–2370.
Patanwala, A.E., Norris, C.J., Nix, D.E., Kopp, B.J., Erstad, B.L., 2009. Vancomycin Dosing for Pneumonia in Critically Ill Trauma Patients. J. Trauma: Injury, Infection & Critical Care 67, 802–804.
Rybak, M.J., Lomaestro, B.M., Rotscahfer, J.C., Moellering, R.C., Craig, W.A., Billeter, M., Dalovisio, J.R., Levine, D.P., 2009. Vancomycin Therapeutic Guidelines: A Summary of Consensus Recommendations from the Infectious Diseases Society

of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin. Infect. Dis. 49, 325–327.
Rybak, M.J., Le, J., Lodise, T.P., Levine, D.P., Bradley, J.S., Liu, C., Mueller, B.A., Pai, M.P., Wong-Beringer, A., Rotschafer, J.C., Rodvold, K.A., Maples, H.D., Lomaestro, B.M., 2020. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatr. Am. J. Health-Syst. Pharm. 77, 835–863.
Sánchez, J.L., Dominguez, A.R., Lane, J.R., Anderson, P.O., Capparelli, E.V., Cornejo-Bravo, J.M., 2010. Population pharmacokinetics of vancomycin in adult and geriatric patients: Comparison of eleven approaches. Int. J. Clin. Pharmacol. Ther. 48, 525–533.