ORIGINAL ARTICLE

Single-dose and Steady-state Pharmacokinetics of Vancomycin in Critically Ill Patients Admitted to Medical Intensive Care Unit of India

Nitin B Mali[1], Siddharth P Deshpande[2], Poorwa P Wandalkar[3], Vishal A Gupta[4], Niteen D Karnik[5], Nithya J Gogtay[6], Gita Nataraj[7], Preeti R Mehta[8], Urmila Thatte[9]

Abstract

Rationale: Vancomycin remains the standard of care for gram-positive bacterial infections, though there are significant developments in newer antibacterial agents. Efficacy can be improved by linking pharmacokinetic with pharmacodynamic principles, thus leading to optimum antibiotic exposure. There is scarcity of pharmacokinetic data in Indian intensive care unit (ICU) population.

Materials and methods: Fifteen subjects with suspected or proven gram-positive bacterial infection of either gender between 18 years and 65 years of age were enrolled. Vancomycin at the dose of 1 g every 12 hours was administered over 1-hour period and pharmacokinetic assessments performed on blood samples collected on days 1 and 3. Vancomycin concentrations were measured on validated liquid chromatography mass spectrometry method. Pharmacokinetic parameters were calculated using Winnonlin (Version 6.3; Pharsight, St. Louis, MO).

Results: The mean $C_{max,}$ elimination half-life, $AUC_{0-12hours}$, volume of distribution, and clearance of single dose were 36.46 µg/mL (±14.87), 3.98 hours (±1.31), 113.51 µg/mL (±49.51), 52.01 L (±31.31), and 8.90 mL/minute (±3.29), respectively, and at steady state were 40.87 µg/mL (±19.29), 6.27 hours (±3.39), 147.94 µg/mL (±72.89), 56.39 L (±42.13), and 6.98 mL/minute (±4.48), respectively. The elimination half-life increased almost two-fold at steady state. The steady state mean AUC_{0-24} was 295.89 µg/mL (±153.82). Out of 45 trough levels, 32 (71.11%) concentrations were below recommended range.

Conclusion: Recommended $AUC_{0-24hours}$ and trough concentrations were not achieved in majority of patients with current dosing, suggesting reevaluation of current vancomycin dosing. Individualized treatment based on close monitoring of vancomycin serum concentrations in critically ill patients is imperative.

Keywords: Critically ill, Methicillin resistance *Staphylococcus aureus*, Pharmacokinetics–pharmacodynamics, Single and steady state, Vancomycin.

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Introduction

Vancomycin, is a glycopeptide antibiotic discovered during the middle of 19th century and is still considered as a first-line therapy for serious infections caused by methicillin resistance *Staphylococcus aureus* (MRSA).[1,2] Intensive care units are considered as the epicenters for nosocomial infections which are resistant to most of the antibiotics; hence, the use of systemic antibiotics including vancomycin is very high. Inappropriate use of systemic antibiotics increases antibiotic resistance, length of ICU stay, treatment cost, mortality, and morbidity rate.[3–6]

In India, the proportion of MRSA pathogen has increased from 29% in 2009 to 47% in 2014,[7] and minimum inhibitory concentration (MIC) of vancomycin is also increasing.[8,9] This necessitates rational use of vancomycin. Pharmacokinetics–pharmacodynamics (PK–PD) assessment and therapeutic drug monitoring (TDM) of vancomycin have been recommended for better clinical outcome and dosing optimization. Various PK–PD studies have showed that 0–24 hours area under the curve (AUC) to MIC ratio of ≥400 is strongly associated with good clinical outcome. It is also recommended that the trough concentrations should always be maintained above 10 µg/mL to avoid development of resistance and for serious infections such as bacteremia, endocarditis, osteomyelitis, and meningitis and hospital-acquired pneumonia trough concentration should be 15–20 µg/mL.[2,10,11]

Despite being an old antibiotic, vancomycin pharmacokinetics (PK) data in critically ill patients are limited and there are no data

[1–3,6,9]Department of Clinical Pharmacology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India

[4,5]Department of Medicine, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India

[7,8]Department of Microbiology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India

Corresponding Author: Urmila Thatte, Department of Clinical Pharmacology, Seth Gordhandas Sunderdas Medical College and King Edward Memorial Hospital, Mumbai, Maharashtra, India, Phone: +91 9820198462, e-mail: urmilathatte@gmail.com

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Conflict of interest: None

in Indian population. During our recent observational study,[12] we observed that vancomycin use is 23.23% in medical ICU without support of therapeutic drug monitoring services and evidence of pk data on vancomycin. Hence, present prospective single dose and steady state PK study was conducted in patients with suspected or proven gram-positive bacterial infections admitted to medical ICU.

Materials and Methods

Study Design and Duration

This was a single center, single arm, prospective, single dose, and steady state PK study. Study was conducted over the period of 9 months from December 2015 to August 2016 in adult subjects admitted to medical ICU.

Study Sites

Department of Medicine and Clinical Pharmacology of a Tertiary Care Medical College and Hospital.

Ethics

Study was initiated after obtaining Institutional Ethics Committee approval. A written informed consent was obtained from all the subjects or legally acceptable representative before performing any study related activity. Study was prospectively registered with Clinical Trial Registry of India with registration number CTRI/2015/11/006393.

Study Participants

Subjects of either gender aged between 18 years and 65 years with suspected or proven gram-positive infection and requiring vancomycin (empirically or proven Gram positive bacterial infection) at the dose of 1 g every 12 hours were considered for the study. Subjects with creatinine clearance (CL_{CR}) <50 mL/minute,[13] already receiving vancomycin therapy, hypersensitivity to vancomycin hydrochloride, or its excipients were excluded.

Study Procedure

Demographics (age, gender, and body weight), serum creatinine, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Gram's stain and culture (for blood or any other appropriate body fluid specimen), antibiotic sensitivity, and MIC for vancomycin were performed prior to initiation of vancomycin therapy.

Vancomycin Treatment

For the study purpose, vancomycin hydrochloride vials from the same batch which were available on hospital schedule (free of cost to the subject) were used throughout study period. Vancomycin at the dose of 1 g every 12 hours was administered via infusion pump over a period of 1 hour.

Blood Sampling

Blood samples (2 mL in a heparinized test tube) were collected from central line on day 1 (single dose) and day 3 (steady state, 48 hours) following the initiation of vancomycin hydrochloride injections, prior to dose administration (0 hour) and at 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours postdrug administration. Predose samples were also collected on days 2, 4, 5, 6, and 7. The plasma was separated and stored at −80°C for pending analysis.

Safety Assessment

All adverse events (AEs)/serious adverse events (SAEs) with reference to below definitions were noted during entire the study duration.[14]

Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

SAE or Serious Adverse Drug Reaction

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

Estimation of Vancomycin by Liquid Chromatography-tandem Mass Spectrometry

A validated bioanalytical liquid chromatography mass spectrometry (LCMS) method for the estimation of vancomycin from plasma samples was used.[15,16] Vancomycin and internal standard (phenacetin) were extracted by solid-phase extraction technique using MCX 1 cc, 30 mg cartridges. Separation of components was performed on C18 column using acetonitrile:ammonium formate:formic acid (60:40:0.1%) as a mobile phase on ultra-fast liquid chromatography (Prominence, Shimadzu, Japan). Quantification was performed using the LCMS API 2000 (Applied Biosystems, MDX Sciex, Toronto, Canada) by multiple reaction monitoring transitions from 725 (diprotonated molecule with actual molecular weight 1449.265 g/mol) to 144.0 and 180.10 to 110.10 for vancomycin and internal standard, respectively. The spiked plasma drug concentrations were linear over the range of 0.259–100 µg/mL. The intraday and interday precision and accuracy was <15% deviation.

Statistical Analysis

No formal sample size calculation was done and a total of 15 subjects were enrolled. Pharmacokinetic parameters were derived by noncompartment modeling[17] using Winnonlin (Version 6.3; Pharsight, St. Louis, MO). The trapezoidal approach was used to estimate AUC and clearance. The Matzke equation was used to estimate vancomycin clearance for each subject.[18] Area under the curve was performed from 0 hour to 12 hours; hence, the $AUC_{0–24\ hours}$ was calculated by doubling of $AUC_{0–12}$.[19]

All statistical analysis was done on Statistical Package for the Social Sciences (SPSS) software version 20 (IBM, Armonk, NY, USA). Continuous numerical variables (such as CL_{CR}, APACHE II score, and all pk parameters) and categorical variables (such as age, gender, and weight) were assessed for the normality using the Kolmogorov–Smirnov test. Normally distributed data were expressed as mean ± SD, and that not normally distributed was presented as median (range).

Results

Demographics

A total of 15 subjects were enrolled (12 males and 3 females) with a median age of 30.00 years (18, 64) and a mean weight of

Table 1: Demographics of participants in the study

Subject ID	*Age (years)*	*Sex*	*Weight (kg)*	*APACHE II score*	*Creatinine clearance (mL/minute)*	*Clinical diagnosis*
1	25	Male	65	0	103.1	Guillain–Barré syndrome
2	18	Male	59	6	66.37	Organophosphorus poisoning
3	61	Male	54	16	59.25	Guillain–Barré syndrome
4	31	Male	62	18	84.47	Tuberculous meningitis
5	28	Male	72	12	100.8	Herpes simplex encephalitis
6	55	Male	74	17	96.02	Guillain–Barré syndrome
7	20	Male	54	12	100	Seizure disorder
8	64	Male	69	22	94.68	Intracranial bleed
9	22	Male	82	0	161.26	Left middle cerebral artery infarct
10	34	Female	58	9	72.58	Cerebral venous thrombosis
11	30	Male	56	14	77.78	Tetanus
12	30	Female	52	2	61.39	Organophosphorus poisoning
13	23	Female	48	8	79.42	Pulmonary thromboemboly
14	59	Male	68	4	66.11	Left-sided community acquired pneumonia
15	56	Male	74	10	86.33	Right-sided community acquired pneumonia
Mean	37.06 (±16.72), median = 30 (18, 64)	Males = 12, females = 3	63.13 (±9.81)	10.00 (±6.75)	87.30 (±25.24)	

63.13 kg (±9.81). The mean APACHE II score and mean CL_{CR} was 10.00 (±6.75) and 87.30 mL/minute (±25.24), respectively. Single-dose PK was performed on 15 subjects and steady state PK was done in 12 subjects due to 2 deaths and a consent withdrawal prior to day 3. A total of 13 subjects received vancomycin for suspected gram-positive bacterial infection and 2 subjects received for proven methicillin-resistant coagulase-negative staphylococci (MRCoNS) infection with vancomycin MIC of 1.5 µg each. Demographics of each individual are presented in Table 1.

Pharmacokinetic Parameters

A wide interindividual variability in pharmacokinetic parameters of single dose and steady state was observed. The elimination half-life ($t_{1/2}$) increased almost two-fold at steady state and was statistically significant ($p = 0.024$). The mean maximum concentration (C_{max}), $t_{1/2}$, AUC from 0 hour to 12 hours ($AUC_{0–12\ hours}$), volume of distribution (Vd), and clearance (CL) after single dose were 36.46 µg/mL (±14.87), 3.98 hours (±1.31), 113.51 µg/mL (±49.51), 52.01 L (±31.31), and 8.90 mL/minute (±3.29), respectively, and at steady state were 40.87 µg/mL (±19.29), 6.27 hours (±3.39), 147.94 µg/mL (±72.89), 56.39 L (±42.13), and 6.98 mL/minute (±4.48), respectively. The steady-state mean AUC from 0 hour to 24 hours ($AUC_{0–24\ hours}$) was 295.89 µg/mL (±153.82) and only three subjects achieved $AUC_{0–24}$ of >400 µg at steady state. Individual pharmacokinetic parameters have been depicted in Table 2 and mean concentrations following single dose and steady state at various time points are shown in Figure 1.

A total of 45 trough levels were measured, of these 32 (71.11%) concentrations were below the recommended range of 10–20 µg/mL, 11 (24.44%) were within range, and 2 (4.45%) concentrations were above the recommended value. The details of trough concentrations are also presented in Figure 2.

None of the study subject experienced any AE related to vancomycin dosing and infusion. However, three subjects died where the causes of death were type II respiratory failure, ventricular tachycardia with autonomic dysfunction in case of tetanus septic shock, and septicemia in a clinical case of pulmonary thromboembolism during postnatal care, respectively. One subject denied to give blood samples post day 2 of study drug administration; hence, this subject was withdrawn from the steady-state pharmacokinetic assessment.

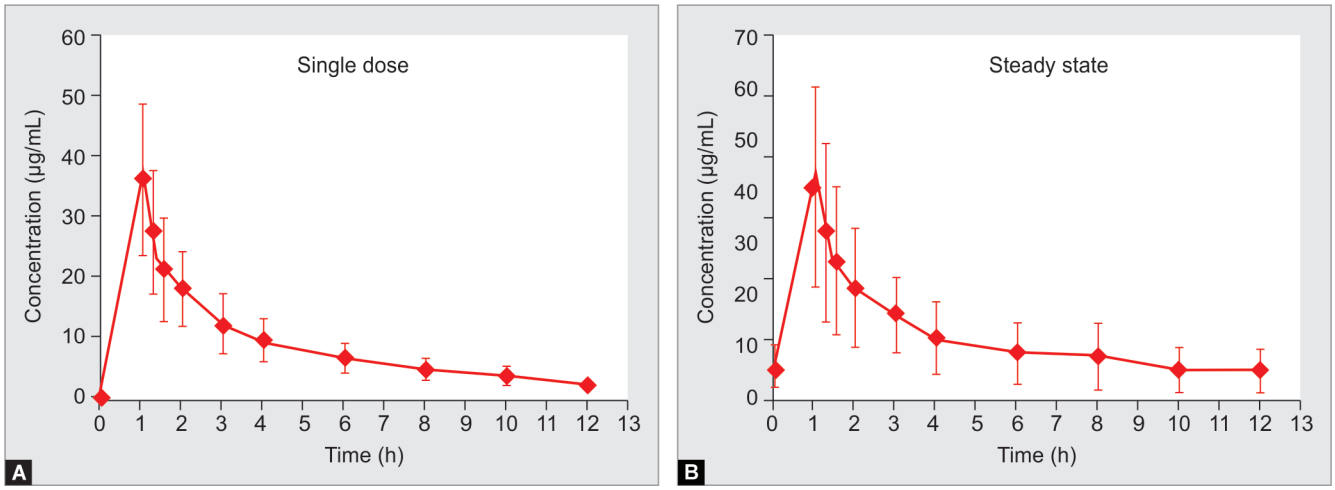
Table 2: Summary of single-dose and steady-state pharmacokinetic parameters

Pharmacokinetic parameter	*Single-dose PK value*	*Steady-state PK value*
C_{max} (µg/mL)	36.47 (±14.87)	40.87 (±19.29)
C_{min} (µg/mL)	3.99 (±3.07)	5.46(±3.84)
T_{max} (hour)	1.02 (±0.06)	1.04 (±0.14)
$T_{1/2}$ (hour)	3.98 (±1.31)	6.27 (±3.39)
$AUC_{0–12}$ (µg/mL)	113.52 (±49.19)	147.94 (±72.89)
$AUC_{0–\infty}$ (µg/mL)	129.49 (±54.73)	206.58 (±132.12)
Vd (L)	52.01 (±31.31)	56.39 (±42.13)
CL (mL/minute)	8.90 (±3.29)	6.98 (±4.48)
Steady state $AUC_{0–24}$ (µg/mL)	NA	295.89 (±153.82)
$AUC_{0–24/MIC}$ (MRCoNS)	NA	193.82 (±125.79)

PK, pharmacokinetics; C_{max}, maximum concentration; C_{min}, minimum concentration; T_{max}, maximum time; $T_{1/2}$, elimination half-life; $AUC_{0–12}$, area under concentration–time curve from 0 hour to 12 hours; $AUC_{0–\infty}$, area under concentration–time curve from 0 to ∞; Vd, volume of distribution; CL, clearance; steady state $AUC_{0–24}$, steady-state area under concentration–time curve from 0 hour to 24 hours; $AUC_{0–24/MIC}$, area under concentration–time curve from 0 hour to 24 hours/minimum inhibitory concentration; MRCoNS, methicillin-resistant coagulase-negative staphylococci

Discussion

Understanding the pharmacokinetic and pharmacodynamic properties of antibiotics in critically ill patients is important due to different pathophysiologies. Vancomycin is being used since its discovery; however, PK–PD data in critically ill patients are limited. To our knowledge, this is a first Indian study conducted in



Figs 1 and B: Single-dose ($n = 15$) and steady-state ($N = 12$) concentration plot of vancomycin. Data are presented as the mean and standard deviation

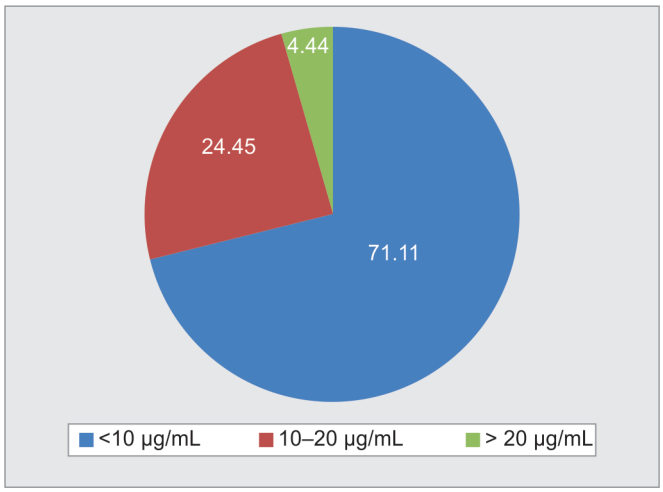


Fig. 2: Vancomycin trough concentrations

critically ill subjects to assess the single dose and steady-state PK of vancomycin and a wide interindividual variability was observed in pharmacokinetic parameters in this population. The recommended dose (1 g every 12 hours) infused over 1 hour was well-tolerated by all subjects compared to the short duration of vancomycin which is known to be associated with many AEs.[10,20]

The C_{max} achieved at single dose and steady state in our study is comparable with those reported in ill patients and lower than those reported in healthy volunteers.[21–23] The minimum concentration (C_{min}) at single dose (3.99 µg/mL ±3.07) and steady state (5.46 µg/mL ±3.84) after administration of 1 g of vancomycin every 12 hours in ill subjects is comparatively lower than the healthy volunteers (7.9 µg/mL ±1.7 at steady state).[21] In present study, at steady state, volume of distribution increased by 7.76% (from 52.01 L to 56.39 L), clearance decreased by 21.57% (from 8.90 mL/minute to 6.98 mL/minute), and half-life ($t_{1/2}$) increased almost two-fold, i.e., from 3.98 hours (±1.31) to 6.27 hours (±3.39) with stable CL_{CR}; however, these are statistically insignificant (except half-life). Our findings are in-line to the study of Polard et al.; however, they observed significant increase in (around 30%) steady-state volume of distribution, decrease in (around 30%) steady state clearance of vancomycin and two-fold increase in half-life.[22] The increase in the vancomycin volume of distribution in ICU patients could be because of increased volume of extracellular fluids caused by microvascular damage and tissue edema induced by sepsis.[22,24–26] However, vancomycin is not highly protein bound (binding is around 50%); hence, it is unlikely that protein variability would affect its extravascular binding.[27,28] It was also advocated that the homeostatic response to acute cardiovascular failure may also increase the vancomycin distribution because of fluid retention; however, this association could not be evaluated in our study, since none of the enrolled subjects had any cardiovascular event.[27] It has been stated that the decrease in clearance at steady state may because of decrease in extrarenal (metabolic or biliary excretion) clearance of vancomycin and/or a modification in renal tubular secretion or reabsorption; however, there is lack of direct evidence reported in humans.[22,29] Single-dose and steady-state half-lives achieved in our study are almost similar to the study conducted by Polard et al. with similar study population. These findings are also comparable with patients with normal renal function and shorter than patients with renal impairment.[22,30]

It has been recommended that the AUC_{0-24}/MIC ratio of ≥400 should be achieved for good clinical outcome.[10,11,31] In present study, two subjects with MRCoNS achieved low AUC_{0-24}/MIC ratio of 282.76 and 104.87 with an MIC of 1.5 µg and only 3 subjects achieved AUC_{0-24} of ≥400.

Peak concentrations of vancomycin have little importance, since bactericidal activity of vancomycin is independent of peak serum concentration. Also, calculating AUC/MIC is cumbersome since it involves serial vancomycin concentrations; therefore, trough concentrations are recommended as a surrogate marker.[10] It was observed that the around 70% concentrations were below recommendations and only 25% achieved in targeted range with current vancomycin dosing. Similar study in ill patients conducted by Dedkaew et al. and Shahrami et al. also found that the ≥50% patients had subtherapeutic vancomycin concentrations.[23,32] Hence, individualization of vancomycin dosing is imperative to achieve good clinical outcome and to avoid resistance. It is also recommended that the vancomycin administration frequency may increase to determine the maintenance dose and dosing interval in critically ill patients with similar degree of renal function.[23]

Limitations

Present study conducted in only normal renal function population; therefore, pharmacokinetic findings of this study may not be applicable to patients with renal impairment.

Conclusion

Wide interindividual variability was observed in pharmacokinetic parameters between ill patients, and changes in clearance, half-life, and volume of distribution over the course of vancomycin therapy were also seen. Recommended $AUC_{0-24hours}$ and trough concentrations were not achievable in majority of patients with current vancomycin dosing at 1 g every 12 hours. Therefore, individual vancomycin dosing based on close monitoring of vancomycin serum concentrations is suggested in critically ill patients.

References

1. Levine DP. Vancomycin: a history. Clin Infect Dis 2006;42(Suppl 1): S5–S12. DOI: 10.1086/491709.
2. Vandecasteele SJ, De Vriese AS, Tacconelli E. The pharmacokinetics and pharmacodynamics of vancomycin in clinical practice: evidence and uncertainties. J Antimicrob Chemother 2013;68(4):743–748. DOI: 10.1093/jac/dks495.
3. Del Mar Fernandez De Gatta Garcia M, Revilla N, Calvo MV, et al. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. Intensive Care Med 2007;33(2):279–285. DOI: 10.1007/s00134-006-0470-5.
4. Revilla N, Martín-Suárez A, Pérez MP, et al. Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/pharmacodynamic simulation. Br J Clin Pharmacol 2010;70(2):201–212. DOI: 10.1111/j.1365-2125.2010.03679.x.
5. Sarin MSK, Vadivelan M, Bammigatti C. Antimicrobial therapy in the intensive care unit. Indian J Clin Pract 2013;23(10):601–609.
6. Cantón R, Horcajada JP, Oliver A, et al. Inappropriate use of antibiotics in hospitals: the complex relationship between antibiotic use and antimicrobial resistance. Enferm Infecc Microbiol Clin 2013;31(Suppl 4): 3–11. DOI: 10.1016/S0213-005X(13)70126-5.
7. Indian Network for Surveillance of Antimicrobial Resistance (INSAR) Group I. Methicillin resistant staphylococcus aureus (MRSA) in india: prevalence & Susceptibility pattern Indian network for surveillance of antimicrobial resistance (INSAR) group, india. Indian J Med Res 2013;137:363–369.
8. Praharaj I, Sujatha S, Chandra Parija S. Phenotypic & genotypic characterization of vancomycin resistant enterococcus isolates from clinical specimens. Indian J Med Res 2013;138:549–556.
9. Phukan C, Lahkar M, Ranotkar S, et al. Emergence of vanA gene among vancomycin-resistant enterococci in a tertiary care hospital of north - east India. Indian J Med Res 2016;143(3):357–361. DOI: 10.4103/0971-5916.182627.
10. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the american society of health-system pharmacists, the infectious diseases society of America, and the society of infectious diseases pharmacists. Am J Health Syst Pharm 2009;66(1):82–98. DOI: 10.2146/ajhp080434.
11. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant staphylococcus aureus infections in adults and children. Clin Infect Dis 2011;52(3):1–38. DOI: 10.1093/cid/ciq146.
12. Mali NB, Deshpande SP, Karnik ND, et al. Multicentric, prospective, observational antibacterial utilization study in Indian tertiary referral centers. Indian J Crit Care Med 2018;22(10):723–729. DOI: 10.4103/ijccm.IJCCM_197_18.
13. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31–41. DOI: 10.1159/000180580.
14. https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf.
15. Zhang T, Watson DG, Azike C, et al. Determination of vancomycin in serum by liquid chromatography-high resolution full scan mass spectrometry. J Chromatogr B Anal Technol Biomed Life Sci 2007;857(2):352–356. DOI: 10.1016/j.jchromb.2007.07.041.
16. Food and Drug Administration (2001) Guidance for Industry: Bioanalytical method validation. (https://www.fda.gov/downloads/drugs/guidances/ucm368107.pdf).
17. Gabrielsson J, Weiner D. Non-compartmental analysis. Computational toxicology. Methods Mol Biol 2012;929:377–389. DOI: 10.1007/978-1-62703-050-2_16.
18. Matzke GR, Kovarik JM, Rybak MJ, et al. Evaluation of the vancomycin clearance: creatinine-clearance relationship for predicting vancomycin dosage. Clin Pharm 1985;4:311–315.
19. Blot S, Koulenti D, Akova M, et al. Does contemporary vancomycin dosing achieve therapeutic targets in a heterogeneous clinical cohort of critically ill patients? Data from the multinational DALI study. Crit Care 2014;18(3):1–11. DOI: 10.1186/cc13874.
20. Marinho DS, Huf G, La FB, et al. The study of vancomycin use and its adverse reactions associated to patients of a Brazilian university hospital. BMC Res Notes 2011;4(1):1–6. DOI: 10.1186/1756-0500-4-236.
21. Healy DP, Polk RE, Garson ML, et al. Comparison of steady-state pharmacokinetics of two dosage regimens of vancomycin in normal volunteers. Antimicrob Agents Chemother 1987;31(3):393–397. DOI: 10.1128/AAC.31.3.393.
22. Polard E, Le Bouguin V, Le Corre P, et al. Non steady state and steady state PKS Bayesian forecasting and vancomycin pharmacokinetics in ICU adult patients. Ther Drug Monit 1999;21(4):395–403. DOI: 10.1097/00007691-199908000-00003.
23. Dedkaew T, Cressey TR, Punyawudho B, et al. Pharmacokinetics of vancomycin in critically ill patients in Thailand. Int J Pharm Pharm Sci 2015;7(9):232–237.
24. Van DR, Vree TB. Intensive care medicine pharmacokinetics of antibiotics in critically ill patients. Trauma 1990; 235–238.
25. Triginer C, Izquierdo I, Fernfindez R, et al. Intensive care medicine gentamicin volume of distribution in critically ill septic patients. Intensive Care Med 1990;16:303–306. DOI: 10.1007/BF01706354.
26. Tod M, Padoin C, Minozzi C, et al. Population pharmacokinetic study of isepamicin with intensive care unit patients. Antimicrob Agents Chemother 1996;40(4):983–987. DOI: 10.1128/AAC.40.4.983.
27. Power BM, Forbes AM, van PV, et al. Pharmacokinetics of drugs used in critically ill adults. Clin Pharmacokinet 1998;34(1):25. DOI: 10.2165/00003088-199834010-00002.
28. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 2006;42(Suppl 1):S35–S39. DOI: 10.1086/491712.
29. Leader WG, Chandler MHH, Castiglia M. Pharmacokinetic optimisation of vancomycin therapy. Clin Pharmacokinet 1995;28(4):327–342. DOI: 10.2165/00003088-199528040-00005.
30. Rodvold KA, Blum RA, Fischer JH, et al. Vancomycin pharmacokinetics in patients with various degrees of renal function. Antimicrob Agents Chemother 1988;32(6):848–852. DOI: 10.1128/AAC.32.6.848.
31. Moise-Broder PA, Forrest A, Birmingham MC, et al. Pharmacodynamics of vancomycin and other antimicrobials in patients with staphylococcus aureus lower respiratory tract infections. Clin Pharmacokinet 2004;43(13):925–942. DOI: 10.2165/00003088-200443130-00005.
32. Shahrami B, Najmeddin F, Mousavi S, et al. Achievement of vancomycin therapeutic goals in critically ill patients: early individualization may be beneficial. Crit Care Res Pract 2016; 1–7. DOI: 10.1155/2016/1245815.