

Therapeutic drug monitoring of vancomycin in neurosurgery patients, from trough concentration to area under the curve: a retrospective single center cohort study in a tertiary hospital

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Abstract

Objective: To evaluate the effect of therapeutic drug monitoring (TDM) of vancomycin in neurosurgery patients.

Methods: In this retrospective, single-center cohort study, data were collected from patients administered vancomycin after neurosurgery during 2020. Intervention by a pharmacist using an area under the curve (AUC)-based strategy for TDM of vancomycin was started on 1 July 2020. The trough concentration was monitored previously. Data regarding basic demographics, vancomycin application, and TDM were collected and analyzed.

Results: Ninety and 155 samples were included in the non-intervention and intervention groups, respectively. No difference in baseline characteristics was detected. After intervention, the attainment rate of vancomycin TDM was significantly increased from 36.7% to 52.3%. The intervention resulted in an increased daily vancomycin dose (28.9 vs. 26.7 mg/kg/day), a more reasonable sample extraction time (sixth vs. ninth dose), reductions in dose adjustments (37.4% vs. 54.4%) and preventative applications (66.7% vs. 52.3%), and no difference in kidney function impact. The intervention group had a shorter hospital stay.

Conclusions: Intervention by a clinical pharmacist using an AUC-based strategy for vancomycin TDM can provide benefits other than pharmacokinetic attainment in neurosurgery patients.

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Further prospective multi-center studies are needed to establish standardized intervention measures and evaluation indicators.

Keywords

Vancomycin, therapeutic drug monitoring, neurosurgery, trough concentration, area under the curve, pharmaceutical care

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Introduction

Vancomycin is one of the most commonly used antibacterial agents after neurosurgery and plays an important role in the prevention and treatment of common postoperative infections in neurosurgery patients. As a drug that has been on the market for more than 60 years, therapeutic drug monitoring (TDM) of vancomycin has been widely performed. The previous guideline¹ recommended monitoring on the basis of the trough concentration. For example, for methicillin-resistant *Staphylococcus aureus* (MRSA) infection, the recommended trough concentration is 10 to 20 mg/L, and the recommended concentration for severe infection is 15 to 20 mg/L. In 2020, the American Society of Health-System Pharmacists, Infectious Diseases Society of America, Pediatric Infectious Diseases Society, and Society of Infectious Diseases Pharmacists issued a new guideline recommending TDM of vancomycin on the basis of the ratio of the area under the curve (AUC) over 24 hours to the minimum inhibitory concentration (AUC/MIC).² When the MIC of MRSA is determined to be 1 mg/L using broth microdilution methods, a target AUC between 400 and 600 mg*hour/L is suggested for invasive MRSA infections in adults and children according to the clinical efficacy and safety data. The Chinese Pharmacological

Society later issued a new guideline, suggesting that TDM of vancomycin can be based on the trough concentration or AUC/MIC.³ Although trough concentration monitoring has been implemented in our neurosurgery department for several years, it is still worthwhile to explore new monitoring methods, especially because many studies have reported that the trough concentration of vancomycin often fails to meet the standard among neurosurgery patients.⁴⁻⁶ In addition, surgeons are relatively unfamiliar with AUC-based monitoring and do not know how to perform, calculate, or adjust dosing strategy. Therefore, the pharmacy department of our hospital assigned a clinical pharmacist to perform an antibiotic stewardship program for vancomycin in the neurosurgery department. The purpose of this study is to analyze the effectiveness of TDM of vancomycin before and after intervention by a clinical pharmacist.

Materials and methods

This is a retrospective cohort study reported according to the STrengthening the Reporting of OBservational Studies in Epidemiology (STROBE) statement.⁷ Because this study is a retrospective analysis, ethical approval was not required. Trough concentration monitoring of vancomycin was recommended but not required

in the Neurosurgery Department of the First Medical Center of PLA General Hospital, and intervention by a pharmacist was not performed before July 2020. After the publication of new therapeutic monitoring guidelines for vancomycin use in treating serious MRSA infections,^{2,3} a pharmacist was assigned to perform TDM and to calculate the AUC of vancomycin in patients for the neurosurgery department.

Data collection, grouping, and definition

Data were retrospectively collected from patients in the Neurosurgery Department of the First Medical Center of PLA General Hospital who received vancomycin after neurosurgery from January 2020 to December 2020. Data regarding basic demographics, vancomycin application, and TDM were collected and analyzed. Only the first TDM sample of each patient was included. The data were divided into non-intervention and intervention groups according to whether patients received intervention from the pharmacist, and the trough concentration or AUC was used as the evaluation index. The inclusion criteria included use of vancomycin for more than 48 hours and performance of TDM of vancomycin within the course of therapy via trough concentration monitoring or calculation of the AUC on the basis of the trough and peak concentrations. The exclusion criteria included pediatric patients, measurement of the vancomycin trough concentration before the third dose, and missing more than 50% of the data. The Cockcroft–Gault Formula was used to calculate the creatinine clearance rate (CCr), and augmented renal clearance (ARC) was defined as a $CCr \geq 130$ mL/minute.⁸ The therapy type was classified as preventative, i.e., no evidence of infection or pathogenic detection; empiric, which referred to infection without pathogenic detection; or targeted, i.e., infection with Gram-positive

bacteria. We have de-identified all patient details in this study.

Intervention strategy

Intervention by the pharmacist was performed after prescription of the drug and included suggestions regarding reducing unnecessary preventative medication, optimization of the dose regimen, timely monitoring reminders, AUC calculation, and suggestions regarding dosing adjustment. Attainment of vancomycin TDM was defined as a trough concentration between 10 and 20 mg/L or an AUC between 400 and 600 mg*hour/L. AUC calculation was performed on the basis of trough and peak concentrations using an online tool (vancomycin calculator, <https://clincalc.com/vancomycin/>).

Outcomes

The primary outcome of this study was the attainment rate of vancomycin TDM. The secondary outcomes included dose rationalization, defined as complying with the recommended dosage of 15 mg/kg q12h; the rate of achieving a reasonable monitoring time, defined as 48 hours after the first dose; the need for therapy adjustment; the incidence of renal impairment, defined as acute renal injury according to the Kidney Disease Improving Global Outcome guideline; and the length of hospital stay.

Statistical analysis

The mean and standard deviation and the median and interquartile range were used to assess normally distributed quantitative variables and skewed variables. The Kruskal–Wallis U test and chi-square or Fisher's exact test were used, as appropriate, to compare continuous and categorical data, respectively. The relationship between intervention by the pharmacist and the vancomycin TDM attainment rate was

evaluated using a logistic regression model by adjusting for confounding variables, which were selected on the basis of a p value < 0.05 in the univariate analysis and clinical relevance. The statistical software package R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) was used in all analyses, and a value of $p < 0.05$ was considered statistically significant.

Results

A total of 251 vancomycin TDM samples were included in this study. The trough concentration was used as a measurement indicator from January 2020 to June 2020. Ninety-six samples were collected during this period, and six samples with more than 50% of data missing were excluded. Ninety samples were included in the non-intervention group. AUC-based vancomycin monitoring was performed from July 2020 to December 2020 after intervention by a pharmacist. A total of 155 samples with no missing data were included in the

intervention group (Figure 1). The baseline characteristics of patients are shown in Table 1. No difference was observed in sex, age, height, weight, body mass index, baseline CCr, and ARC rate between the two groups. The total ARC rate of our cohort was 32.2%.

Table 2 shows the vancomycin attainment rate of the two groups, which was defined as a trough concentration between 10 and 20 mg/L in the non-intervention group and an AUC between 400 and 600 mg*hour/L in the intervention group. The intervention group showed a significantly increased attainment rate, 52.3% vs. 36.7%, $p = 0.026$. The daily dose was higher in the intervention group than in the non-intervention group, 28.9 mg/kg/day vs 26.7 mg/kg/day, $p = 0.004$. After the intervention, the sample extraction time was reduced to the sixth dose before measurement, compared with the ninth dose in the non-intervention group, $p < 0.001$. Fewer patients required therapeutic adjustment in the intervention group, 37.4% vs. 54.4%, $p = 0.014$.

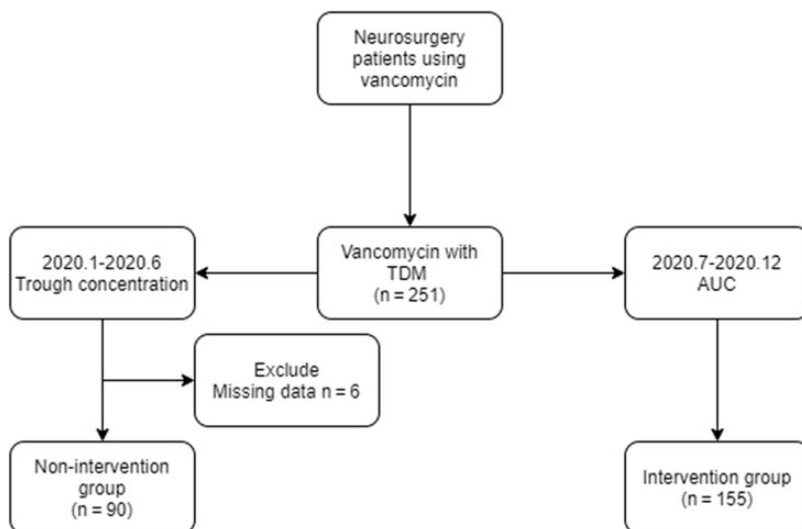


Figure 1. Flow chart of the research. TDM, therapeutic drug monitoring; AUC, area under the curve.

Table 1. Baseline characteristics of patients.

| Variables | Total (n = 245) | Non-intervention group (n = 90) | Intervention group (n = 155) | p |
|------------------------------|----------------------|---------------------------------|------------------------------|-------|
| Sex, male, n (%) | 154 (62.9) | 61 (67.8) | 93 (60) | 0.281 |
| Age, years, median (IQR) | 52.0 (36.0, 62.0) | 48.0 (35.0, 58.8) | 53.0 (37.0, 63.0) | 0.14 |
| Height, cm, median (IQR) | 170.0 (162.0, 175.0) | 170.0 (165.0, 173.0) | 170.0 (161.0, 176.0) | 0.256 |
| Weight, kg, median (IQR) | 70.0 (60.0, 78.0) | 69.0 (60.0, 78.0) | 70.0 (60.0, 78.0) | 0.624 |
| BMI, median (IQR) | 24.0 (21.8, 27.0) | 24.3 (22.0, 27.1) | 23.9 (21.8, 26.9) | 0.751 |
| CCr, mL/minute, median (IQR) | 113.7 (88.9, 143.1) | 115.4 (91.8, 138.9) | 110.6 (86.2, 143.2) | 0.591 |
| ARC, n (%) | 79 (32.2) | 25 (27.8) | 54 (34.8) | 0.318 |

IQR, interquartile range; BMI, body mass index; CCr, creatinine clearance rate; ARC, augmented renal clearance.

Table 2. Therapeutic drug monitoring of vancomycin and outcomes of patients.

| Variables | Total (n = 245) | Non-intervention group (n = 90) | Intervention group (n = 155) | p |
|--|-------------------|---------------------------------|------------------------------|--------|
| Attainment, n (%) | 114 (46.5) | 33 (36.7) | 81 (52.3) | 0.026 |
| Daily dose mg/kg/day, median (IQR) | 27.8 (23.5, 33.3) | 26.7 (22.6, 32.3) | 28.9 (25.1, 34.5) | 0.004 |
| Therapy course, days, median (IQR) | 7.0 (4.0, 12.0) | 7.0 (4.0, 13.0) | 7.0 (4.0, 12.0) | 0.81 |
| Dose before measurement | 8.0 (4.0, 12.0) | 9.0 (6.0, 14.0) | 6.0 (4.0, 10.1) | <0.001 |
| Dose adjustment, n (%) | 107 (43.7) | 49 (54.4) | 58 (37.4) | 0.014 |
| Therapy type, n (%) | | | | 0.01 |
| Preventative | 141 (57.6) | 60 (66.7) | 81 (52.3) | |
| Empiric | 55 (22.4) | 21 (23.3) | 34 (21.9) | |
| Targeted | 49 (20.0) | 9 (10) | 40 (25.8) | |
| Trough concentration, mg/mL, median (IQR) | 9.9 (6.3, 15.1) | 8.7 (6.3, 14.6) | 10.0 (6.2, 15.4) | 0.664 |
| SCr before intervention, μ mol/L, median (IQR) | 62.6 (49.1, 76.9) | 63.1 (52.8, 76.9) | 61.2 (46.5, 76.9) | 0.326 |
| SCr after intervention, μ mol/L, median (IQR) | 58.6 (47.3, 73.3) | 58.3 (48.3, 72.0) | 58.9 (46.0, 73.4) | 0.839 |
| LOS, days, median (IQR) | 23.0 (18.0, 35.0) | 25.0 (20.0, 36.0) | 22.0 (16.0, 34.5) | 0.016 |

IQR, interquartile range; SCr, serum creatinine; LOS, length of hospital stay.

The empiric and targeted therapy rates were significantly increased in the intervention group, $p=0.01$. The length of hospital stay was shorter in the intervention group, 25 days compared with 22 days in the non-intervention group ($p=0.016$). The change in renal function before and after vancomycin treatment was not different between the two groups. The attainment rate of vancomycin TDM was associated with intervention by the pharmacist (crude odds ratio 1.89; 95% confidence interval 1.11–3.22

$p=0.019$). Intervention significantly increased the attainment rate, even after adjusting for possible confounding factors (adjusted odds ratio 2.53; 95% CI 1.31–4.86 $p=0.005$), as shown in Table 3.

Discussion

Vancomycin is one of the oldest antibacterial drugs, and TDM of vancomycin has been clinically implemented for many years. Vancomycin has been widely used

Table 3. Association between pharmacist intervention and the attainment rate of vancomycin therapeutic drug monitoring.

| Variable | Attainment, n (%) | p |
|------------------------|-------------------|-------|
| Total | 114 (46.5) | |
| Non-intervention group | 33 (36.7) | |
| Intervention group | 81 (52.3) | |
| Crude OR 95% CI | 1.89 (1.11–3.22) | 0.019 |
| Adjusted OR 95% CI | 2.53 (1.31–4.86) | 0.005 |

Covariates: all of the variables in Table 1 and Table 2.
OR, odds ratio; CI, confidence interval.

in neurosurgery patients, and a certain understanding of vancomycin TDM exists among neurosurgeons. However, misunderstandings still exist in clinical practice. After the new guidelines were published in 2020,^{2,3} surgeons had difficulty in understanding and using relatively complicated pharmacokinetic parameters such as the AUC or AUC/MIC. In our study, after intervention by the pharmacist, the attainment rate of vancomycin TDM was significantly increased. Additionally, other advantages included an increased daily vancomycin dose, a more reasonable sample extraction time, the need for fewer adjustments, a reduced proportion of preventative application of vancomycin, and no difference in kidney function impact.

Joaquim F Monteiro reported that the clearance rate of vancomycin was significantly elevated in neurosurgery patients.⁹ Regarding the dosing strategy for vancomycin in neurosurgery patients, its augmented clearance rate should be considered, and TDM should be performed as needed. Similar to a previous report,¹⁰ in our study, approximately one-third (32.2%) of patients exhibited ARC. Therefore, the attainment rate of vancomycin TDM in this cohort was only 46.5%. Another factor that greatly affected vancomycin exposure was the low daily dose, although the dose was increased from 26.7 mg/kg/day

to 28.9 mg/kg/day after intervention. This dosage is lower than that recommended by the guideline,² and few surgeons understand the concept of a loading dose, which led to the establishment of 1 g of vancomycin every 12 hours as a universal dose without consideration of the patient's weight. Compliance with TDM of vancomycin has been a key point of pharmaceutical intervention, but real-world data are not optimistic. Jane E Carland found that suboptimal vancomycin TDM remains a problem despite the availability of local and international guidelines.¹¹ Only 24% of vancomycin courses included in that study involved administration of a loading dose. Additionally, in 72% of cases, the loading dose was lower than recommended, and in 34% of cases, the maintenance dose was also lower than recommended. Real vancomycin trough concentrations were extracted in only 14% of samples, and in more than half, dose adjustment was not implemented. Tatjana Van Der Heggen reported that 68% of adults, 76% of children, and 52% of neonates in their study had sub-therapeutic vancomycin concentrations.¹² Some patients, especially children and neonates, never reached the target concentrations, even after dose adjustment. The authors also emphasized the importance of vancomycin TDM awareness for all healthcare professionals involved in patient care. However, in our study, intervention by the pharmacist was not allowed before prescription of vancomycin. To address this problem, future studies should focus on interventions performed before a prescription is issued.

Many studies have shown the relationship between the AUC of vancomycin and acute kidney injury¹³ and have shown that AUC monitoring can result in a decreased risk of acute kidney injury compared with trough concentration monitoring.¹⁴ However, implementation of AUC monitoring is difficult. Wesley D Kufel reported

that the most common challenge encountered by institutions performing AUC-based monitoring was pharmacist and/or provider unfamiliarity.¹⁵ Additionally, it must be noted that TDM of vancomycin has been the subject of some controversy. Thomas J Dilworth suggested that AUC monitoring for empiric therapy is futile, and a loading dose may decrease the workload of monitoring for broad application.¹⁶ Prospective studies have also found no significant correlation between pharmacokinetic/pharmacodynamic indices and the clinical or microbiological efficacy of vancomycin in Chinese patients.^{17,18} However, considering the severity of post-neurosurgery infection, the prevalence of preventative and empiric treatment because of difficulties in pathogen culture and the risk-benefit balance, and the relative lack of awareness of rational application of vancomycin by neurosurgeons, which is demonstrated by the lack of a loading dose, low dose exposure, and unwillingness to stop treatment, TDM of vancomycin should be used to ensure a therapeutic effect and reduce additional damage. Trough concentration monitoring is an option that is still recommended by the Chinese guideline; however, some hospitals cannot properly perform trough concentration monitoring or, particularly, AUC monitoring.³ Furthermore, treatment failure has been reported when the trough concentration of vancomycin is within the treatment range but the AUC/MIC fails to meet the target.¹⁹ Thus, it is reasonable to use an AUC-based monitoring strategy with the help of a pharmacist performing pharmacokinetic calculations and interpretation of the results.²⁰

In our study, intervention by a pharmacist was performed after prescription of vancomycin and was based on the principle of antimicrobial stewardship.²¹ Education and training were performed weekly for doctors, including suggestions about

reducing unnecessary preventative medication and the importance of vancomycin concentration monitoring. Dose regimen optimization was performed for every vancomycin prescription, and an electronic record reminder was sent to doctors on the monitoring day. AUC calculation and adjustment suggestions were completed in a timely manner and sent to doctors via the electronic system. Although we did not perform a prospective study, and intervention was not performed before surgeons administered a prescription, the intervention partially achieved the targets of rationalization of the treatment dose and timelier TDM via communication between the pharmacist and surgeons. Required dose adjustments were reduced after intervention by the pharmacist, and the length of the hospital stay was also reduced during the intervention period, although this may not have been solely because of the intervention of the pharmacist. These results demonstrate the necessity of involving clinical pharmacists in TDM of vancomycin.

Limitations

This study has several limitations. First, this is a retrospective cohort study, and therefore, similar to other retrospective analyses, the potential for residual confounding factors may exist. We adjusted as many covariates that may be related to the outcomes as possible. Second, because of the lack of mortality and since more than half of patients were receiving preventative therapy, it was impossible to evaluate the efficacy of vancomycin using indicators of infection. We used the treatment course, rate of need for adjustment, and length of hospital stay as alternative indicators. Finally, this is a single-center study with a relatively small sample size. Further prospective multi-center studies should be conducted to provide additional evidence for clinical decision-making.

Conclusion

Real-world vancomycin application and TDM is not ideal for neurosurgery patients. Intervention by clinical pharmacists using an AUC-based strategy instead of the trough concentration can increase the attainment rate of vancomycin TDM. This method can also promote rationalization of the vancomycin dosage, optimize the monitoring time, reduce requirements for adjustment, decrease preventative application, and shorten the average length of hospital stay.


Declaration of conflicting interest

The authors declare no conflict of interest in preparing this article.

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