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Effect of augmented renal clearance on the therapeutic drug monitoring of vancomycin in patients after neurosurgery

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Abstract

Objective: To study the effect of augmented renal clearance (ARC) on vancomycin therapeutic drug monitoring in patients undergoing neurosurgery.

Methods: A retrospective observational analysis was conducted in a neurosurgery department from January 2019 to June 2019. Patients undergoing vancomycin therapeutic drug monitoring were assigned to the normal renal function or ARC group. The baseline characteristics, vancomycin therapeutic drug monitoring data, and prognosis were compared and analyzed.

Results: In total, 104 patients were enrolled, including 78 and 26 patients in the normal renal function and ARC groups, respectively. There were significant differences in age, weight, creatinine clearance, the vancomycin treatment duration, the total dose, the trough concentration, and the trough concentration achievement rate between the two groups. Prognosis did not differ between the two groups. The trough concentration achievement rate in the ARC group was only 19.23%.

Conclusion: For young, obese, or otherwise healthy patients undergoing neurosurgery, attention should be paid to the possibility of ARC and the need for individualized dose adjustment based on the results of therapeutic drug monitoring.

Keywords

Augmented renal clearance, neurosurgery, vancomycin, therapeutic drug monitoring, renal function, infection

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Introduction

Augmented renal clearance (ARC), defined as a creatinine clearance rate (CCr) of $\geq$130 mL/minute/1.73 m^2, is the enhancement of glomerular filtration caused by pathophysiologic factors.[1] Patients undergoing neurosurgery are usually healthy with normal liver and kidney function. Therefore, the influence of renal function on the drug dosage focuses on acute kidney injury, and little attention is paid to ARC. Vancomycin is the first-line treatment for gram-positive bacterial infection after neurosurgery,[2] and its trough concentration is directly related to its therapeutic efficacy.[3] Vancomycin is mainly excreted by the kidneys, and ARC has been confirmed as one cause of treatment failure caused by insufficient vancomycin blood concentrations.[4] The purpose of this study was to investigate the occurrence of ARC in patients after neurosurgery and its effect on vancomycin blood concentrations and treatment efficacy.

Materials and methods

A retrospective observational analysis was conducted in the Neurosurgery Department of First Medical Center of Chinese PLA General Hospital.

Inclusion and exclusion criteria

Patients treated with vancomycin after neurosurgery from January 2019 to June 2019 were included in this retrospective analysis.

The inclusion criteria were as follows: (1) adult patients (>18 years old) with normal liver and kidney function; (2) use for vancomycin for more than 72 h; and (3) the trough concentration of vancomycin was tested.

The exclusion criteria were as follows: (1) hepatic or renal insufficiency; (2) pregnancy in women, (3) younger than 18 years old; (3) less than three drug doses were received; and (4) incomplete data.

All patients' demographic data, including sex, age, weight, pre- and post-medication routine examination results, pathogen data (if available), kidney function, pre-medication serum albumin, the dosage and duration of vancomycin, the trough concentration, the length of hospital stay, and prognosis, were collected.

Grouping

Patients were divided into the normal renal function and ARC groups according to CCr before the start of treatment. CCr > 130 mL/minute/1.73 m^2 was defined as ARC and calculated using the Cockcroft–Gault formula. The target trough concentration of vancomycin was 10 to 20 mg/L.

Statistical methods

Statistical analysis was conducted using SPSS Statistics version 24.0 (IBM Corporation, Armonk, NY, USA). Normally distributed data were expressed as the mean $\pm$ SD, whereas non-normally distributed data were expressed as the median (Q25, Q75). Cross-group comparisons were made using Student's *t*-test and the Mann–Whitney U test. Moreover, the chi-squared test was applied to compare classified variables. Bivariate correlation analysis was performed using the Pearson or Spearman correlation test. $P < 0.05$ indicated statistical significance.

Ethics statement

The study was approved by the medical Ethics Committee of Chinese PLA General Hospital, Beijing, China. The requirement for informed consent was waived because of the retrospective nature of the study.

Results

Basic characteristics of the patients

In total, 104 patients were included in the study, including 78 patients in the normal group and 26 patients in the ARC group (Figure 1). Age ($P = 0.000$), weight ($P = 0.028$), and CCr before vancomycin treatment ($P = 0.008$) were significantly different between the groups (see Table 1).

Vancomycin therapeutic drug monitoring

The results of vancomycin therapeutic drug monitoring are presented in Table 2. The total dosage and duration of vancomycin treatment were 18 g (8, 28) and 8 days (4, 13), respectively, in the normal group, versus 12 g (7.1, 17.8) and 5 days (3, 10), respectively, in the ARC group. There were significant differences in the total dosage ($P = 0.040$) and duration of treatment ($P = 0.040$) between the two groups. Therapeutic drug monitoring was performed 5 days (3, 7) after the start of treatment in the normal group, versus 3.5 ± 1.7 days in the ARC group ($P = 0.000$). The mean vancomycin trough concentrations in the two groups were 10.72 mg/L (6.97, 16.55) in the normal group and 6.45 mg/L (3.72, 8.64) in the ARC group ($P < 0.001$).

The vancomycin trough concentration results are presented in Table 3. The rate of achievement of the target trough concentration was 41.03% in the normal group, compared with 19.23% in the ARC group. In addition, 14.10% of patients in the normal group had trough concentrations that exceeded the recommended range (>20 mg/L), compared with 0% in the ARC group. The proportions of patients in the three vancomycin trough concentration groups (<10, 10–20, and >20 mg/L) were significantly different between the groups ($P < 0.001$). Furthermore, the trough concentration was correlated with age ($\rho = 0.236$, $P = 0.017$) and CCr before administration ($\rho = -0.281$, $P = 0.004$).

Treatment and prognosis

Vancomycin was used in most empirical anti-infective treatments in patients after neurosurgery. Because few related

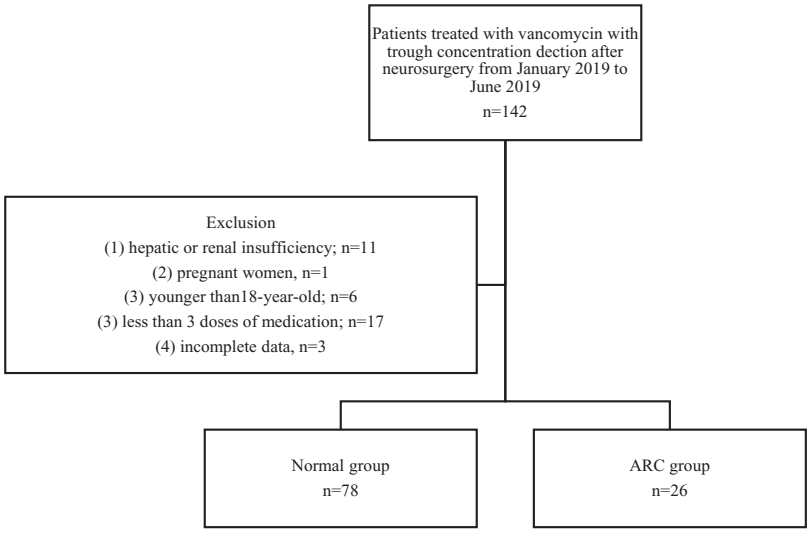

Figure 1. Flowchart of patient inclusion and exclusion.

Table 1. Basic characteristics of the patients.

Characteristics	Normal group (n = 78)	ARC group (n = 26)	*P*
Gender (male:female)	53:25	18:8	
Age (years)	56 (45, 62)	33 (26, 46)	<0.001#
Weight (kg)	69 (59, 76)	75 (62, 90)	0.028#
Before			
CCr (mL/minute/1.73 m^2)	99.8 (87.5,119.8)	168.4 (148.5,193.2)	0.008#
serum albumin (g/L)	31.21 ± 3.05	30.37 ± 5.11	0.730
Diseases			
Cerebral tumor	40	15	
Stroke	27	7	
TBI	11	4	
Complications			
Liver disease	0	0	
Kidney disease	0	0	
Hypertension	21	6	
Cardiopathy	2	0	
Diabetes	4	3	
Others	2	0	
Treatment indication			
Empirical	65	22	
Targeted	6	3	
Prophylactic	7	1	

*$P < 0.05$, Student's *t*-test; #$P < 0.05$, Mann–Whitney's U test.
CCr, creatinine clearance rate; TBI, traumatic brain injury.

Table 2. Monitoring of vancomycin treatment drugs.

	Normal group (n = 78)	ARC group (n = 26)	*P*
Total dosage (g)	18 (8, 28)	12 (7.1, 17.8)	0.040#
Single dose (g)	0.87 ± 0.43	1.28 ± 0.52	0.559
Duration of treatment (days)	8 (4,13)	5 (3,10)	<0.001#
Monitoring day	5 (3,7)	3.5 ± 1.7	<0.001#
Trough concentration (mg/L)	10.72 (6.97, 16.55)	6.45 (3.72, 8.64)	0.040#

#$P < 0.05$, Mann–Whitney's U test.

pathogens (gram-positive bacteria) were detected, clinical and laboratory indicators were used as prognostic criteria. There were no significant differences between the two groups regarding these indicators. No adverse reactions such as renal impairment occurred during treatment (see Table 4).

Discussion

ARC is a common phenomenon among patients undergoing neurosurgery

It has been reported that ARC is associated with the following variables: age < 50 years,

male sex, high diastolic blood pressure, trauma, sequential organ failure assessment score ≤ 4, absence of diabetes, and ICU stay.[5] According to previous reports, the incidence of ARC in different studies among critically ill patients was approximately 14% to 80%. The difference is mainly attributable to the different definitions of ARC and possible differences in patient selection, such as the inclusion or exclusion of patients with renal impairment.[6] Among patients undergoing neurosurgery, the incidence of ARC varies by disease, complications, the time course of treatment, and other factors. Considering the relatively high incidence of ARC, it might influence the pharmacokinetics of drugs, especially those excreted through the kidneys such as vancomycin. We focused on post-neurosurgery patients undergoing vancomycin therapeutic monitoring and excluded those with previous histories of liver or kidney disease. In this patient group, 25% had ARC, and patients with ARC tended to be younger and weigh more. Similarly as most patients undergoing elective neurosurgery, few patients in our study had dysfunction in other organs. Our research also confirmed previous finding that in neurosurgery departments, ARC may be a common phenomenon that should be monitored, especially among young, overweight, and previously healthy patients.

Table 3. Vancomycin trough concentration.

Trough concentration	Normal group (n = 78)	ARC group (n = 26)
<10 mg/L	34 (43.59%)	21 (80.77%)
10–20 m g/L	32 (41.03%)	5 (19.23%)
>20 mg/L	11 (14.10%)	0 (0%)

Effect of ARC on vancomycin therapeutic drug monitoring

Vancomycin is a water-soluble glycopeptide antibacterial agent that serves as the first-line treatment for post-surgical infection. In total, 80% to 90% of the vancomycin dose is excreted through the kidneys, and ARC has been reported to have a significant effect on the pharmacokinetics of vancomycin.[7] Guidelines recommend that a vancomycin steady-state trough concentration of 10 to 15 mg/L (for patients with mild-to-moderate infection) or 15 to 20 mg/L (for patients with severe infection) is required during the treatment of MRSA infection.[3] This study set 10 to 20 mg/L as the target

Table 4. Treatment and prognosis.

		Normal group (n = 78)	ARC group (n = 26)	*P*
Before	Temperature (°C)	38 (37.4, 38.6)	38.1 ± 0.8	0.114
	WBC ($\times 10^9$)	12.63 (10.69, 16.57)	11.9 ± 3.8	0.333
	NEUT (%)	83.9 (79.3, 89.1)	83.1 (77.2, 87.0)	0.231
	CCr (mL/minute/1.73 m^2)	99.8 (87.5, 119.8)	168.4 (148.5, 193.2)	0.008#
After	Temperature (°C)	36.9 (36.4, 37)	37.1 (36.8, 37.9)	0.257
	WBC ($\times 10^9$)	10.9 ± 3.6	10.0 ± 2.4	0.121
	NEUT (%)	80.4 (74.6, 87.2)	76.9 (71.5, 81.2)	0.122
	CCr (mL/minute/1.73 m^2)	111.8 ± 24.6	193.3 ± 59.4	0.009*
Length of hospital stay (days)		24 (20, 36)	21 (15.5, 29.25)	0.050

*$P < 0.05$, Student's *t*-test; #$P < 0.05$, Mann–Whitney's U test.

Before, before the start of vancomycin treatment; After, at the end of vancomycin treatment; WBC, white blood cell count; NEUT; neutrophil count; CCr, creatinine clearance rate.

trough concentration range. The rate of achievement of the vancomycin steady-state trough concentration was generally low in this study, but fewer patients achieved the target in the ARC group. The results illustrated that the blood concentration of vancomycin was measured earlier in the ARC group, indicating that this group of patients (mostly obese patients) received more attention regarding whether the concentration target was achieved. The individual vancomycin dose was higher in the ARC group, but the duration of treatment and total dose were smaller in this group. This indicates that in the medical records, most patients were directly switched to other drugs (such as linezolid) after the blood concentration did not reach the target.

Effect of ARC on anti-infection treatment

Empirical therapy is commonly used in post-neurosurgery patients because of difficulties in obtaining positive culture results from cerebrospinal fluid.[8] Empirical treatment was commonly used in both groups. Few patients in this study were infected with gram-positive bacteria. Thus, we used clinically related indicators to determine the prognosis. There were no differences in prognosis and side effect rates between the normal and ARC groups. The possible reasons were as follows: (1) few patients had a definite pathogenesis and evidence of Gram-positive bacterial infection; (2) no patients used vancomycin alone, and other drugs targeting anti-Gram-negative bacteria may have influenced the prognosis; (3) our sample size was relatively small, and further research is needed to clarify the findings; and (4) patients in the ARC group were switched other drugs after failing to achieve the target vancomycin concentration.

Limitations

Because of the nature of retrospective observational analysis, there are unavoidable limitations in this study. (1) Similarly as most studies, we only focused on the vancomycin trough concentration at a certain time point. Previous reports illustrated that ARC may dynamically change at different stages of the disease. Thus, monitoring may be needed during the entire process of drug administration. (2) Because of the small sample size of the study, it was difficult to further analyze the independent risk factors of the vancomycin concentration. Further research is needed to investigate the independent risk factors of the vancomycin concentration and ARC. (3) The pharmacodynamics of vancomycin was not examined in this research. However, very few studies have described the pharmacokinetics/pharmacodynamics of vancomycin in neurosurgery departments because of the lack of microbiological results. Vancomycin is commonly used as an empirical treatment, especially in hospitals with rigorous antimicrobial stewardship. With the assistance of newly developed gene sequencing technology, we hope to solve this problem in the future.

In summary, ARC may be a common phenomenon among patients undergoing neurosurgery, especially among young, overweight, or previously healthy patients. ARC may influence the vancomycin trough concentration. Furthermore, ARC may have similar effects on other drugs excreted by the kidneys, making their levels difficult to detect using therapeutic drug monitoring.[9] Thus, patients with ARC should be identified as early as possible, and drug treatment may need to be adjusted according to the individualization of therapeutic drug monitoring, renal function, and the characteristics of the drug itself.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Cook AM and Hatton-Kolpek J. Augmented Renal Clearance. *Pharmacotherapy* 2019; 39: 346–354.
2. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis* 2017; 64: e34–e65.
3. Ye ZK, Chen YL, Chen K, et al. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. *J Antimicrob Chemother* 2016; 71: 3020–3025.
4. Moser C, Lerche CJ, Thomsen K, et al. Antibiotic therapy as personalized medicine - general considerations and complicating factors. *APMIS* 2019; 127: 361–371.
5. Wu CC, Tai CH, Liao WY, et al. Augmented renal clearance is associated with inadequate antibiotic pharmacokinetic/pharmacodynamic target in Asian ICU population: a prospective observational study. *Infect Drug Resist* 2019; 12: 2531–2541.
6. Carrié C, Chadefaux G, Sauvage N, et al. Increased β-Lactams dosing regimens improve clinical outcome in critically ill patients with augmented renal clearance treated for a first episode of hospital or ventilator-acquired pneumonia: a before and after study. *Crit Care* 2019; 23: 379.
7. Chu Y, Luo Y, Ji S, et al. Population pharmacokinetics of vancomycin in Chinese patients with augmented renal clearance. *J Infect Public Health* 2020; 13: 68–74.
8. Sharma S, Acharya J, Banjara MR, et al. Comparison of acridine orange fluorescent microscopy and gram stain light microscopy for the rapid detection of bacteria in cerebrospinal fluid. *BMC Res Notes* 2020; 13: 29.
9. Hobbs AL, Shea KM, Roberts KM, et al. Implications of Augmented Renal Clearance on Drug Dosing in Critically Ill Patients: A Focus on Antibiotics. *Pharmacotherapy* 2015; 35: 1063–1075.