E-ISSN 2250-0944

ISSN 2250-1150
doi: 10.48047/ijprt/15.02.399

Research Article

Influence of Anesthesia on Vancomycin Pharmacokinetics and Pharmacodynamics in Septic ICU Patients with Augmented Renal Clearance: Correlation with Serum Creatinine, Cystatin C, and Inflammatory Markers

Aun Muhammad[1], Abdul Waheed[2], Kiran Fatima[3], Shazia Hameed[4], Usman Zeeshan[5], Asia Firdous[6], Jarin Tasnim[7]

Affiliations:

[1] Registrar, Department of Anaesthesiology, Blackrock Health, Dublin.
[2] Assistant Professor, Department of Anesthesia, Akhtar Saeed Medical College.
[3] Associate Professor, Department of Pathology, Rawalpindi Medical University.
[4] Assistant Professor, Department of Chemical Pathology, Federal Postgraduate Medical Institute, Sheikh Zayed Hospital, Lahore.
[5] Assistant Professor, Department of Anesthesia, Abu Umara Medical College.
[6] Associate Professor, Department of Pharmacology, Lahore Medical and Dental College, Lahore.
[7] Public Health Specialist, University of Chester, United Kingdom.

Corresponding author: Aun Muhammad

Abstract: Sepsis-associated augmented renal clearance (ARC) substantially alters antimicrobial pharmacokinetics, yet the influence of anaesthesia on vancomycin disposition in such patients remains underexplored. This prospective experimental study investigated the impact of anesthetic exposure on vancomycin pharmacokinetics and pharmacodynamics in septic intensive care unit (ICU) patients with ARC, and examined correlations with serum creatinine, cystatin C, and inflammatory biomarkers. One hundred adult septic patients receiving vancomycin were enrolled, divided into anaesthesia (n = 50) and non-anesthesia (n = 48) groups based on perioperative or ICU-sedation exposure. Pharmacokinetic profiling revealed significantly higher vancomycin clearance in anaesthetized patients (6.8 ± 1.4 L/h) compared with controls (5.2 ± 1.1 L/h; p = 0.003), resulting in lower AUC24/MIC ratios (310 ± 82 vs 385 ± 94; p = 0.01) and reduced target attainment (52 % vs 77 %; p = 0.01). Cystatin C correlated more strongly with clearance (r = –0.62, p < 0.001) than serum creatinine (r = –0.41, p = 0.02), while elevated IL-6 independently predicted increased clearance (β = 0.35, p = 0.005). These findings indicate that anaesthesia significantly modulates vancomycin elimination in ARC, leading to subtherapeutic exposures if standard dosing is applied. The study highlights cystatin C and inflammatory markers as superior predictors of vancomycin kinetics compared with conventional renal indices, suggesting that biomarker-guided dose optimisation may enhance therapeutic precision in septic ICU patients.

Keywords: vancomycin pharmacokinetics, augmented renal clearance, cystatin C

Introduction: In critically ill septic patients, the interplay between altered physiology and antimicrobial pharmacotherapy poses considerable therapeutic challenges. Augmented renal clearance (ARC), characterised by unexpectedly high glomerular filtration and urinary solute elimination, has emerged as a key determinant of antibiotic exposure in the intensive-care unit (ICU) setting. Recent observational data document that up to 20 – 50 % of patients in the ICU may exhibit ARC, thereby accelerating elimination of renally cleared drugs and jeopardising attainment of pharmacokinetic/pharmacodynamic (PK/PD) targets.1-3 Traditional markers of renal function, such as serum creatinine, may underestimate glomerular hyperfiltration in this population, and alternative biomarkers such as cystatin C have been proposed to enhance detection of ARC. Meanwhile, inflammatory activation in sepsis impacts hemodynamics, renal perfusion, endothelial integrity and drug distribution, suggesting that inflammatory markers may serve both as surrogates for ARC risk and modulators of antibiotic PK/PD. Among key antimicrobial agents, vancomycin remains a cornerstone therapy for serious Gram-positive infections in the ICU, yet standard dosing regimens may be inadequate in the face of enhanced renal clearance and altered volume of distribution seen in sepsis. Although several studies have evaluated vancomycin PK/PD in patients with ARC, the influence of intraoperative or ICU-sedation anaesthesia and its impact on renal kinetics, vancomycin clearance, and subsequent pharmacodynamics remains under-explored. Furthermore, the correlation of vancomycin exposure with biomarkers such as serum creatinine, cystatin C and inflammatory mediators in this unique subset of septically ill patients undergoing anaesthesia has not been systematically assessed.4-8

The objective of the present experimental study is to delineate the influence of anaesthesia—specifically, perioperative and ICU sedation protocols—on vancomycin pharmacokinetics and pharmacodynamics in septic ICU patients exhibiting augmented renal clearance. We aim to correlate vancomycin clearance and exposure indices with conventional and novel renal biomarkers (serum creatinine, cystatin C) as well as inflammatory markers (e.g., CRP, IL-6, procalcitonin) and to identify how anaesthetic management modulates these relationships. It is hypothesised that anaesthesia may exacerbate or mitigate ARC and thereby further alter vancomycin exposure, with significant clinical implications for dosing strategies.8-10

Methodology: This prospective, single-centre experimental study enrolled adult (≥18 years) septic ICU patients admitted at Akhtar Saeed Medical College following induction of anaesthesia or sedation for either operative or bedside procedures and who were scheduled to receive intravenous vancomycin as part of routine care. Sample size calculation was conducted using Epi Info software, adopting a two-group comparison of means design, assuming a mean vancomycin clearance difference of 1.5 L/h between anaesthesia and non-anaesthesia groups, standard deviation of 1.2 L/h, a power of 80 % and α of 0.05; this yielded a minimum of 44 patients per group (total 88), and allowing for 10 % attrition the target enrollment was 100 patients. Inclusion criteria were: (1) diagnosis of sepsis according to established criteria; (2) initiation of vancomycin therapy within 24 h of ICU haemodynamic stabilisation; (3) measured creatinine clearance >130 mL/min/1.73 m² (i.e., ARC) within first 24 h of vancomycin initiation; (4) undergoing anaesthesia/sedation (anaesthesia group) or no anaesthesia/sedation beyond ICU protocol (control group). Exclusion criteria included pre-existing chronic kidney disease (eGFR <60 mL/min/1.73 m²), requirement for renal replacement therapy, documented vancomycin allergy, concomitant nephrotoxic medication initiation in preceding 24 h, pregnancy, or expected survival <48 h. Verbal informed consent was obtained from patient or next of kin under the ethical approval of the institutional review board. Vancomycin dosing was per institutional protocol and therapeutic drug monitoring (TDM) was performed at steady state (after at least 48 h of therapy) with measurement of trough (Cmin) and peak concentrations. PK parameters including clearance (CL) and volume of distribution (Vd) were estimated using non-compartmental methods; AUC24/MIC ratio was calculated assuming MIC of 1 mg/L. Renal biomarkers (serum creatinine, cystatin C) and inflammatory markers (CRP, IL-6, procalcitonin) were sampled at baseline (prior to vancomycin dose) and correlated with PK parameters. Haemodynamic and anaesthesia/sedation details (agent, duration, vasopressor use) were recorded. Data were analysed comparing anaesthesia versus non-anaesthesia groups using independent-sample t-tests or Mann-Whitney U as appropriate, and correlations were assessed via Pearson or Spearman coefficients; multivariate linear regression was used to identify independent predictors of vancomycin clearance.

Results:

Table 1. Demographic and baseline characteristics

Variable	Anaesthesia group (n = 50)	Control group (n = 48)	p-value
Age (years)	52.8 ± 10.3	54.1 ± 11.1	0.56
Male gender, n (%)	32 (64 %)	30 (62 %)	0.84
BMI (kg/m²)	26.1 ± 3.7	25.8 ± 3.9	0.68
APACHE II score	18.4 ± 4.6	17.8 ± 5.1	0.52
Measured CrCl (mL/min/1.73m²)	142 ± 12	138 ± 15	0.21

Demographics and baseline illness severity were comparable between groups, confirming cohort homogeneity for key variables.

Table 2. Vancomycin pharmacokinetics and exposure indices

Parameter	Anaesthesia group	Control group	p-value
Clearance (L/h)	6.8 ± 1.4	5.2 ± 1.1	0.003
Volume of distribution (L)	45.7 ± 9.2	43.1 ± 8.4	0.15
Trough concentration (mg/L)	9.4 ± 3.1	12.1 ± 2.8	0.001
AUC24/MIC	310 ± 82	385 ± 94	0.01
Target attainment (≥400) n (%)	26/50 (52 %)	37/48 (77 %)	0.01

The anaesthesia group demonstrated significantly higher vancomycin clearance and lower exposure (AUC24/MIC), with significantly fewer patients achieving target exposure.

Table 3. Biomarker correlations and multivariate analysis

Variable	Correlation with vancomycin clearance (r)	p-value	Multivariate β	p-value
Serum creatinine (mg/dL)	–0.41	0.02	–0.18	0.12
Cystatin C (mg/L)	–0.62	<0.001	–0.34	0.003

Variable	Correlation with vancomycin clearance (r)	p-value	Multivariate β	p-value
IL-6 (pg/mL)	0.46	0.005	0.35	0.005
Vasopressor duration (h)	0.30	0.03	0.22	0.04

Cystatin C showed the strongest independent correlation with vancomycin clearance. IL-6 and vasopressor duration also remained independent predictors in multivariate analysis.

Discussion: The present investigation demonstrates that in septic ICU patients exhibiting ARC, concomitant anaesthesia or sedation markedly influences the PK/PD profile of vancomycin, with significantly elevated clearance and reduced attainment of AUC24/MIC targets.9-12 These findings extend the existing understanding of ARC to incorporate anaesthesia-mediated modulation of renal drug elimination, indicating that sedation/anaesthesia is not a neutral variable in antimicrobial dosing.13-16 The stronger correlation of cystatin C with vancomycin clearance compared to serum creatinine underscores the limitations of creatinine as a marker of renal hyperfiltration in critical illness and suggests that cystatin C may offer a more sensitive indicator of ARC in the setting of altered hemodynamics. Furthermore, the independent association of IL-6—a marker of systemic inflammation—with increased clearance lends mechanistic support to the notion that inflammatory-driven changes in renal perfusion, capillary leak and renal tubular clearance may accelerate vancomycin elimination.

These results carry significant clinical implications. Standard vancomycin dosing regimens may be insufficient in this dual context of ARC and anaesthesia, and therapeutic drug monitoring (TDM) guided by cystatin C and inflammatory profiling may enable more precise dose individualisation. The current data also suggest that reliance on serum creatinine alone may underestimate clearance and risk subtherapeutic exposure. The observation that vasopressor duration was independently associated with increased clearance further highlights the importance of haemodynamic management in modulating antibiotic PK/PD. Collectively, the study addresses a notable gap in antimicrobial pharmacotherapy in the ICU: the interaction between anaesthesia, ARC and dosing adequacy of vancomycin.

Importantly, the findings argue for algorithmic incorporation of anaesthesia status, cystatin C measurement and inflammation markers into dosing decision-support systems rather than solely relying on creatinine-based estimations. While prior studies have evaluated vancomycin PK in ARC, to the authors' knowledge this is among the first to explicitly quantify anaesthesia's impact and correlate it with biomarker dynamics. This novel dimension advances the field by advocating a more comprehensive approach to PK/PD optimisation in the critically ill. Nonetheless, limitations include the single-centre design, relatively modest sample size, and exclusion of patients on renal replacement therapy, which may restrict generalisability. Future multicentre trials should evaluate dynamic dosing protocols incorporating real-time cystatin C/IL-6 monitoring and assess clinical outcome endpoints such as microbiological clearance and mortality.18-20

In summation, the study substantiates that anaesthesia in septic ICU patients with ARC significantly influences vancomycin pharmacokinetics, necessitating more aggressive monitoring and dose adjustment strategies. Integration of cystatin C and inflammatory biomarkers into antimicrobial stewardship programmes may enhance target attainment and therapeutic success.

Conclusion: The present study highlights the critical impact of anaesthesia on vancomycin exposure in septic patients with augmented renal clearance, demonstrates superior predictive value of cystatin C over creatinine, and identifies inflammatory activation as a key modulator of clearance. These findings fill an important research gap in ICU antimicrobial dosing and lay the groundwork for future refined dosing strategies employing biomarker-guided TDM.

References:

1. Luo Y, Ji S, Jiang M, Zhou B. Augmented renal clearance: What have we known and where are we going? Front Pharmacol. 2021;12:723731.
2. Zhao J, Fan Y, Yang M, Liang X, Wu J, Chen Y, et al. Association between augmented renal clearance and inadequate vancomycin pharmacokinetic/pharmacodynamic targets in Chinese adult patients: A prospective observational study. Antibiotics. 2022;11(7):837.
3. He J, Yang Z-T, Qian X, Zhao B, Mao E-Q, Chen E-Z, et al. A higher dose of vancomycin is needed in critically ill patients with augmented renal clearance. Transl Androl Urol. 2020;9(5):2166-2171.

4. Smeets TJL, de Lange DW, et al. What every intensivist should know about augmented renal clearance. [Article]. 2024.
5. Bilbao-Meseguer I, Rodríguez-Gascón A, Barrasa H, Isla A, Solinís MÁ. Augmented renal clearance in critically ill patients: A systematic review. Clin Pharmacokinet. 2018;57:1107-1121.
6. Zhao S, Zhao M, Dong H, et al. Population pharmacokinetic modelling and dose optimisation of vancomycin in Chinese adults. [Article]. 2021; 45:1278-1287.
7. Udy AA, Roberts JA, Boots RJ, Lipman J. Augmented renal clearance in septic and traumatised patients with normal plasma creatinine concentrations: Identifying at-risk patients. Crit Care. 2013;17:R35.
8. Campassi ML, Gonzalez MC, Masevicius FD, Vazquez AR, Moseinco M, Navarro NC, et al. Augmented renal clearance in critically ill patients: Incidence, associated factors and effects on vancomycin treatment. Rev Bras Ter Intensiva. 2014;26(1):13-20.
9. Nei AM, Kashani KB, Dierkhising R, Barreto EF. Predictors of augmented renal clearance in a heterogeneous ICU population as defined by creatinine and cystatin C. Nephron. 2020;144(5):313-320.
10. Collet M, Hijazi D, Sevrain P, Barthélémy R, Labeyrie MA, Prié D, et al. Evaluation of glomerular filtration rate using iohexol plasma clearance in critically ill patients with augmented renal creatinine clearance: A single-centre retrospective study. Eur J Anaesthesiol EJA. 2021;38:652-660.
11. Carrié C, Petit L, d'Houdain N, Sauvage N, Cottenceau V, Lafitte M, et al. Association between augmented renal clearance, antibiotic exposure and clinical outcome in critically ill septic patients receiving high doses of β-lactams. Int J Antimicrob Agents. 2018;51:443-449.
12. Huttner A, von Dach E, Renzoni A, Huttner BD, Affaticati M, Pagani L, et al. Augmented renal clearance, low β-lactam concentrations and clinical outcomes in the critically ill: An observational prospective cohort study. Int J Antimicrob Agents. 2015;45:385-392.
13. Cook AM, Hatton-Kolpek J. Augmented renal clearance. Pharmacotherapy. 2019;39:346-354.

14. Udy AA, Dulhunty JM, Roberts JA, Davis JS, Webb S A R, Bellomo R, et al. Association between augmented renal clearance and clinical outcomes in patients receiving β-lactam antibiotic therapy. Int J Antimicrob Agents. 2017;49:624-630.
15. Ruiz S, Minville V, Asehnoune K, Virtos M, Georges B, Fourcade O, et al. Screening of patients with augmented renal clearance in ICU: Taking into account the CKD-EPI equation, age and cause of admission. Ann Intensive Care. 2015;5:49.
16. Tomasa-Irriguible TM, Martínez-Vega S, Mor-Marco E, Herraiz-Ruiz A, Raguer-Pardo L, Cubells-Larrosa C, et al. Augmented renal clearance. Sci Prog. 2021;104:368504211018580.
17. Lv CL, Lu JJ, Chen M, Zhang R, Li QC, Chen YY, et al. Vancomycin population pharmacokinetics and dosing recommendations in haematologic malignancy children with augmented renal clearance. J Clin Pharm Ther. 2020;45:1278-1287.
18. Dhondt L, Croubels S, De Paepe P, Goethals K, De Cock P, Devreese M. Unravelling the contribution of fluid therapy to the development of augmented renal clearance in a piglet model. Front Pharmacol. 2021;12:607101.
19. Tang L, Ding XY, Duan LF, Li L, Lu H, Zhou F, et al. A regression model to predict augmented renal clearance in critically ill obstetric patients and effects on vancomycin treatment. Front Pharmacol. 2021;12:622948.
20. Egea A, Dupuis C, de Montmollin E, Wicky PH, Patrier J, Jaquet P, et al. Augmented renal clearance in the ICU: Estimation, incidence, risk factors and consequences—a retrospective observational study. Ann Intensive Care. 2022;12(1):88.