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OPEN PEER REVIEW

Comparison of Pharmacokinetic/Pharmacodynamic Parameters and Clinical Outcomes of Vancomycin Administered in Two Different Dosage Regimens in Patients with Acute Kidney Injury

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1 Original submission

2 comments · 10 Jan 2025 – 3 Feb 2025

Referee 1 Reviewer

REJECT 10 Jan 2025

This study addresses an important and clinically relevant topic regarding vancomycin dosing in patients with acute kidney injury (AKI), particularly those not receiving renal replacement therapy (RRT). However, while the topic of vancomycin dosing in AKI patients is important, it is not a novel area of research. Numerous studies have already explored the pharmacokinetics and dosing of vancomycin in patients with renal impairment, especially in those requiring RRT. The study's focus on patients without RRT does not substantially differentiate it from previous work in this field. Moreover, the methods and tools used (e.g., Cockcroft-Gault equation, AUC/MIC target) are well-established and not innovative. To enhance the novelty, the study could have included new pharmacokinetic models, novel dosing strategies, or innovative methodologies in its design or data analysis.

Absence of Comparison with Other Treatment Approaches: The study lacks a comparison to alternative dosing strategies or newer methods for vancomycin administration. A broader comparison could have highlighted the unique contribution of this research in advancing clinical practice.

Limited Clinical Impact: Despite the findings of higher AUC/MIC ratios in the intervention group, the study does not demonstrate a significant difference in clinical outcomes (e.g., need for renal replacement therapy or mortality rates). This weakens the overall clinical impact of the findings and further raises questions about the novelty and utility of the dosing strategy being tested.
Other weaknesses of the study are as follows:
Sample Size and Statistical Power:
The sample size is relatively small, which limits the power of the statistical tests and may affect the generalizability of the findings.
In Table 1, the age distribution between the two groups shows no significant difference, but the smaller sample size could still lead to Type II errors (false negatives).

Demographic and Renal Function Differences:
The creatinine clearance values between the two groups are not significantly different ($p = 0.14$), which is good for randomization. However, the intervention group (mean age 58.00 ± 18.18 years) and the control group (mean age 66.22 ± 11.91 years) show a noticeable age difference, which could have influenced the pharmacokinetic outcomes, even if the p-value is above the significance threshold.
Sex distribution also varies between the groups, although not significantly ($p = 0.28$). However, age and sex differences could still affect the study outcomes and should be addressed in the discussion.

Lack of Statistical Significance in Secondary Outcomes:
Mortality and need for hemodialysis: Despite significant differences in pharmacokinetic parameters (e.g., AUC and peak concentration) between the groups, secondary outcomes such as mortality ($p = 0.63$) and hemodialysis need ($p = 0.29$) show no significant difference. This raises concerns regarding the clinical relevance of the pharmacokinetic differences observed. It's important to discuss why higher vancomycin levels (AUC/MIC) did not translate into improved clinical outcomes. This might be due to the complexity of AKI, the presence of other confounding factors, or the pharmacodynamic properties of vancomycin in AKI patients.

Clinical Relevance of the Findings:
AUC/MIC: While the intervention group achieved a significantly higher AUC/MIC ($p = 0.005$), it is concerning that neither group reached the therapeutic AUC/MIC target of 400-600 mg·h/L.

Data Interpretation:
Table 2 clearly shows differences in the trough and peak concentrations between the groups, but it is not entirely clear why the higher concentrations in the intervention group did not lead to improved clinical outcomes (i.e., reduced need for hemodialysis or mortality). The study should address possible pharmacodynamic factors (e.g., vancomycin's nephrotoxicity potential, time vs. concentration dependence) that could explain this discrepancy.
While this study tackles an important topic, its novelty is limited, and its clinical impact is inconclusive.

Kaveh Eslami Reviewer

MINOR REVISION 3 Feb 2025

The manuscript presents significant findings on vancomycin pharmacokinetics in AKI patients.
Recommendations:
1. Provide a detailed justification for the chosen sample size, including power calculations or other constraints.
2. Provide the data on pathogens for which vancomycin was used in the study, if available, and indicate what other antibiotics the patients received.
3. It seems your study population was homogenous, but the inclusion/exclusion criteria do not ensure this. I think, based on the small sample size, you had stricter inclusion/exclusion criteria that are not fully described in the manuscript.
4. What is "(ref)" in this part? Is it a reference you missed? "Since patients in the full-dose group achieved higher AUCs but still failed to reach the therapeutic range, it can be inferred that dosing vancomycin every 6 to 8 hours, or using continuous infusion, in critically ill patients with AKI could increase the likelihood of attaining the PD target (ref)."

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reviewer 1

Q1:

Thank you for your thoughtful review and for highlighting important aspects of our manuscript. I would like to clarify that there are significant differences in pharmacokinetics and pharmacodynamics (PKPD) of drugs in the context of dialysis compared to early stages of acute kidney injury (AKI). In dialysis, drug clearance is influenced by factors such as the dialysis membrane, flow rate, and duration of dialysis. In contrast, there is considerable uncertainty surrounding the management of drug dosing in AKI, with most references and guidelines emphasizing the need for frequent drug level evaluations, which can be challenging in our country.

We acknowledge your observation regarding the Cockcroft-Gault (CG) formula. While it is not an innovative approach, we intend to use it in a novel context by applying it to vancomycin clearance, as outlined in our methods section. As you noted, specifics regarding dosing for AKI patients are often derived from chronic kidney disease (CKD) data, which may not adequately reflect the nuances of AKI. For instance, while studies suggest a maintenance dosing of 10-15 mg/kg/day for patients with a GFR between 15 to 50 mL/min, it is crucial to acknowledge the variability in kidney function within this range. Importantly, these dosing recommendations are primarily based on stable chronic kidney impairment rather than AKI.

I completely agree that utilization of PKPD model and urine creatinine clearance are advantageous; however, I would like to highlight that our study faced limitations due to a small sample size, as mentioned in the limitations section of our manuscript. Additionally, the challenges encountered in an open ICU environment, along with the difficulties associated with 24-hour urine collection, raised concerns about potential bias and error in our findings.

I appreciate your understanding of these limitations, and I hope this clarification provides additional context for our methodological choices. These changes provided in introduction and limitation section.

Q2:

Thank you for your valuable feedback. I would like to expound upon my comparison of our method, which administered full doses of vancomycin, to the adjusted dosing based on vancomycin clearance formulations. This adjusted dosing is not a routine practice and distinguishes our study from others, even those involving different drugs. (refer to introduction and method section)

As you are aware, many physicians are hesitant to administer full doses of potentially nephrotoxic drugs like vancomycin to AKI patients. Conversations with experts and a review of vancomycin levels over the past few years in various centers across our country indicate that many patients, even those without AKI, are often undertreated with vancomycin. This issue is particularly pronounced in

patients with renal impairment, where a significant portion of their vancomycin levels were found to be subtherapeutic.

Q3:

I agree that the clinical outcome is important, but I want to emphasize that our study was mostly about the impact of AKI on vancomycin PKPD and clinical outcome was not our focus. During ICU hospitalization, numerous factors may influence mortality that are unrelated to the brief trial of vancomycin dosing.

Q4:

Again, I appreciate your valuable insight. Unfortunately, there were no similar studies available when we designed our trial. Based on the experience of experts at our study center, we observed that approximately 60% of patients receiving vancomycin had subtherapeutic levels. With our trial, we aimed to achieve an 90% success rate in attaining the AUC target. Assuming an alpha of 0.05 and a power of 80%, we estimated that each group would require about 14 patients. As mentioned previously, I concur that a larger sample size would enhance the accuracy and reliability of our findings. However, the patient recruitment process was significantly restricted, as detailed in the methods section. Additionally, the open ICU system posed challenges that contributed to a high rate of participant dropout. The changes provided in method section.

Q5:

Thank you for your constructive feedback, as you pointed out, the p-value was not significant. I believe this aspect is central to our analysis, as the lack of significance in the baseline data supports the validity of the randomization process.

Q6:

Thank you for your insightful comment. I genuinely appreciate your perspective. The emphasis of our trial was primarily on the pharmacokinetic-pharmacodynamic (PKPD) characteristics of vancomycin, rather than the clinical impact, which was not our study’s main objective. As you are well aware, clinical outcomes are influenced by a wide range of factors that extend beyond the scope of our analysis. I hope this clarification addresses your concerns, and I am grateful for your thoughtful feedback.

Q7:

Thank you for your thoughtful review and for highlighting important aspects of our manuscript. As I mentioned earlier, physicians are often hesitant to administer full doses of vancomycin to these patients. We contend that if patients had received the recommended full doses of the drug, administered three times per day, the pharmacokinetic and pharmacodynamic results would have been significantly more robust. Unfortunately, this represents another limitation we encountered in our study. Regarding the sentence you referenced, I would like to clarify that patients who received full doses of vancomycin achieved the higher AUC/MIC more

consistently than those who did not. However, as previously mentioned, there was considerable hesitation among physicians to administer the recommended full doses via a three-times-per-day infusion. Consequently, the total vancomycin levels did not consistently fall within the target range, even in the intervention group. It is important to emphasize, however, that the intervention group did achieve a significantly higher AUC target.

Q8:

Thank you for your continued engagement with our manuscript and for your valuable feedback. I want to assure you that I have provided a comprehensive response to the comment regarding data interpretation in my previous replies. The primary focus of our study was on the pharmacokinetic-pharmacodynamic (PKPD) profile of vancomycin rather than on its clinical impact. Although we utilized the Cockcroft-Gault (CG) method as a base formula for our calculations, it is relevant to note that the specific vancomycin clearance kinetic formula is not routinely applied in clinical practice. Changes provided in introduction and discussion.

Furthermore, our study population, consisting of patients with acute kidney injury (AKI) who did not undergo dialysis, addresses a significant gap in knowledge regarding vancomycin and other drug dosing. This research could have meaningful implications, particularly for underdeveloped and developing countries. I hope this clarification emphasizes the relevance and contributions of our study.

Reviewer 2:

Q1:

Thank you for your thoughtful review and for highlighting important aspects of our manuscript. Unfortunately, there were no similar studies available when we designed our trial. Based on the experience of experts at our study center, we observed that approximately 60% of patients receiving vancomycin had subtherapeutic levels. With our trial, we aimed to achieve an 90% success rate in attaining the AUC target. Assuming an alpha of 0.05 and a power of 80%, we estimated that each group would require about 14 patients. As mentioned previously, I concur that a larger sample size would enhance the accuracy and reliability of our findings. However, the patient recruitment process was significantly restricted, as detailed in the methods section. Additionally, the open ICU system posed challenges that contributed to a high rate of participant dropout. These changes provided in method section.

Q2:

Thank you for your insightful comments regarding our study. I would like to address the limitation you highlighted related to the empirical nature of vancomycin prescriptions. Unfortunately, the majority of vancomycin was prescribed empirically, and many patients were not MRSA culture-positive, which

often led to the early discontinuation of the drug. This aspect does represent a limitation in our study, as vancomycin was typically initiated for conditions like ventilator-associated pneumonia (VAP) or hospital-acquired pneumonia (HAP). Once cultures indicated the presence of gram-negative pathogens, we frequently de-escalated antibiotics, resulting in the discontinuation of vancomycin and subsequent dropout from our study. In contrast, in other settings such as sepsis, vancomycin and overall gram-positive coverage were standard practice in our ICU. For patients with meningitis, particularly those with post-operative conditions, we observed positive MRSA cultures. The other antibiotics prescribed to our patients primarily included carbapenems, colistin, and, occasionally, aminoglycosides for HAP/VAP cases. In the context of meningitis, carbapenems were often combined with colistin (administered intravenously and intraventricularly in post-operative patients). In sepsis cases, the standard regimen typically included carbapenems and, if necessary, colistin alongside vancomycin.

Q3:

Thank you once again for your valuable feedback. Yes, as you noted, to maintain homogeneity in our study, we established strict inclusion and exclusion criteria.

To enroll study, Participants were required:

to be over 18 years of age

have received at least four doses of vancomycin

experiencing ongoing AKI due to any cause, as defined by the KDIGO criteria: an increase in serum creatinine of at least 0.3 mg/dL within 48 hours or a decrease in urine output to less than 0.5 mL/kg/h for at least six hours

not being Pregnant or breastfeeding

Additionally, patients were excluded if:

AKI resolved

they required renal replacement therapy (RRT) for any reason

They experienced infection progression while on vancomycin

There were unplanned changes in vancomycin dosing or withholding of vancomycin during the study period.

I appreciate your understanding of these complexities and their implications for our findings. These changes provided in method section.

Q4:

I apologize for this oversight and acknowledge that it was an editing error on my part. Thank you for your understanding.

2 Revision 1

0 comments

No public comments in this round.