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Letter to editor

Volume of distribution as an early predictor of vancomycin-induced AKI in critically ill patients

Parisa Ghasemiyeh[1,2], Afsaneh Vazin[1], Farid Zand[3], and Soliman Mohammadi-Samani[2,4]

[1]Department of Clinical Pharmacy, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran; [2]Pharmaceutical Sciences Research Center, Shiraz University of Medical Sciences, Shiraz, Iran; [3]Anesthesiology and Critical Care Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran; [4]Department of Pharmaceutics, School of Pharmacy, Shiraz University of Medical Sciences, Shiraz, Iran

To the Editor,

In our previous study, we focused on vancomycin pharmacokinetic in critically ill patients and vancomycin-induced acute kidney injury (AKI) (1). Now, we have new findings regarding the key role of volume of distribution (V_d) in AKI prediction in this group. The changes in vancomycin pharmacokinetic parameters would be expectable in special groups of patients (2). V_d can be calculated through different equations. Eq. 1-3 are based on individualized data obtained from blood sampling and pharmacokinetic analysis (3), while, Eq. 4 is based on data extracted from the population pharmacokinetic (4). V_d can be calculated individually either based on the k values (slope of LnC *vs.* time curve) (Eq. 1 and 2) or independent of k (Eq. 3) (5).

$$V_d(1) = \frac{Cl}{k} \quad \text{(Eq. 1)}$$

$$V_d(2) = \frac{k_0(1-e^{-kt})}{Ck} \quad \text{(Eq. 2)}$$

$$V_d(3) = \frac{Dose}{C_{max} - C_{min}} \quad \text{(Eq. 3)}$$

$$V_d(4) = 0.72\frac{L}{kg} \; if \; eGFR \geq 60$$
$$V_d(4) = 0.9\frac{L}{kg} \; if \; eGFR < 60 \quad \text{(Eq. 4)}$$

While *Cl* is clearance (L/h), *k* is elimination constant (h^{-1}), k_0 is the rate of drug infusion (mg/h), *C* is the vancomycin concentration after the end of infusion time (mg/L), *Dose* is the administered drug (mg), C_{max} and C_{min} are the steady-state peak and trough concentrations, respectively, and *eGFR* is the estimated glomerular filtration rate (ml/min/1.73m^2) (4).

The results of V_d values calculated through the aforementioned equations in the AKI and non-AKI groups are presented in Table 1. V_d values derived from individualized pharmacokinetic assessments (V_d 1, 2, 3) were much lower in the AKI group, while, for V_d 4, the trend was reversed. Therefore, it seems that V_d calculation based on the population data would not be a suitable surrogate for individualized assessment of V_d.

In order to assess the V_d cut-off points to predict vancomycin-induced AKI, receiver operating characteristic (ROC) curve was utilized. Cut-off points, area under the ROC curves (AUCs), sensitivity, and specificity in AKI prediction are summarized in Table 1 and Figure S1. According to the results, the individualized V_d (V_d 1, 2, 3) values could significantly predict vancomycin-induced AKI with adequate sensitivity, specificity, and AUCs. Therefore, V_d values smaller than the cut-off points could lead to vancomycin-induced AKI. However, the V_d values obtained from the population data (V_d 4) showed a reverse trend and also failed to significantly predict AKI occurrence.

Therefore, according to the results of the present study, it seems that the reduced V_d value would be a promising early predictor of vancomycin-induced

Table 1. Comparison of calculated volume of distribution (V_d) values in AKI and non-AKI groups (N=53).

Volume of distribution (V_d)	V_d in AKI group (Mean±SD)	V_d in Non-AKI group (Mean±SD)	Cut-off points for AKI	P-value	Area under the ROC curve (AUC)	Sensitivity (%)	Specificity (%)
V_d (1)	65.77±47.51 L	162.97±211.25 L	≤50.96 L	0.049	0.692	55.56	77.14
V_d (2)	23.27±12.80 L	52.87±34.38 L	≤30.27 L	<0.001	0.829	77.78	80.00
V_d (3)	66.15±46.38 L	149.43±164.40 L	≤83.06 L	0.012	0.733	88.89	56.76
V_d (4)	53.27±9.42 L	48.16±8.39 L	>51.12 L	0.059	0.708	66.67	79.55

AKI. These reduced V_d values can be attributed to the enhanced concentration changes (C_{max}-C_{min}) based on Eq. 3. Also, there are some other biological determining parameters that influence V_d values in patients susceptible to AKI that would be genetically governed in this group of patients, although to date there is not any published data. Interestingly, these results for V_d in patients who developed to AKI were completely different from those with chronic kidney disease (CKD) who have increased V_d values due to the enhanced total body water, hypoalbuminemia, and decreased protein binding (6). In this regard, we proposed early assessment of V_d in vancomycin receiving patients to predict the possible AKI development.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Ethics Statement: This study was reviewed and approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran. (Approval ID No.: IR.SUMS.REC.1398.605). The patients/participants provided their written informed consent to participate in this study.

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Correspondence:
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Soliman Mohammadi-Samani, Pharm.D., Ph.D.,
Professor of Pharmaceutics
School of Pharmacy, Shiraz-Marvdasht Hwy, Karafarin St,
Shiraz, Fars Province 71468 64685, Iran
Email: smsamani@sums.ac.ir

Appendix – Supplementary file

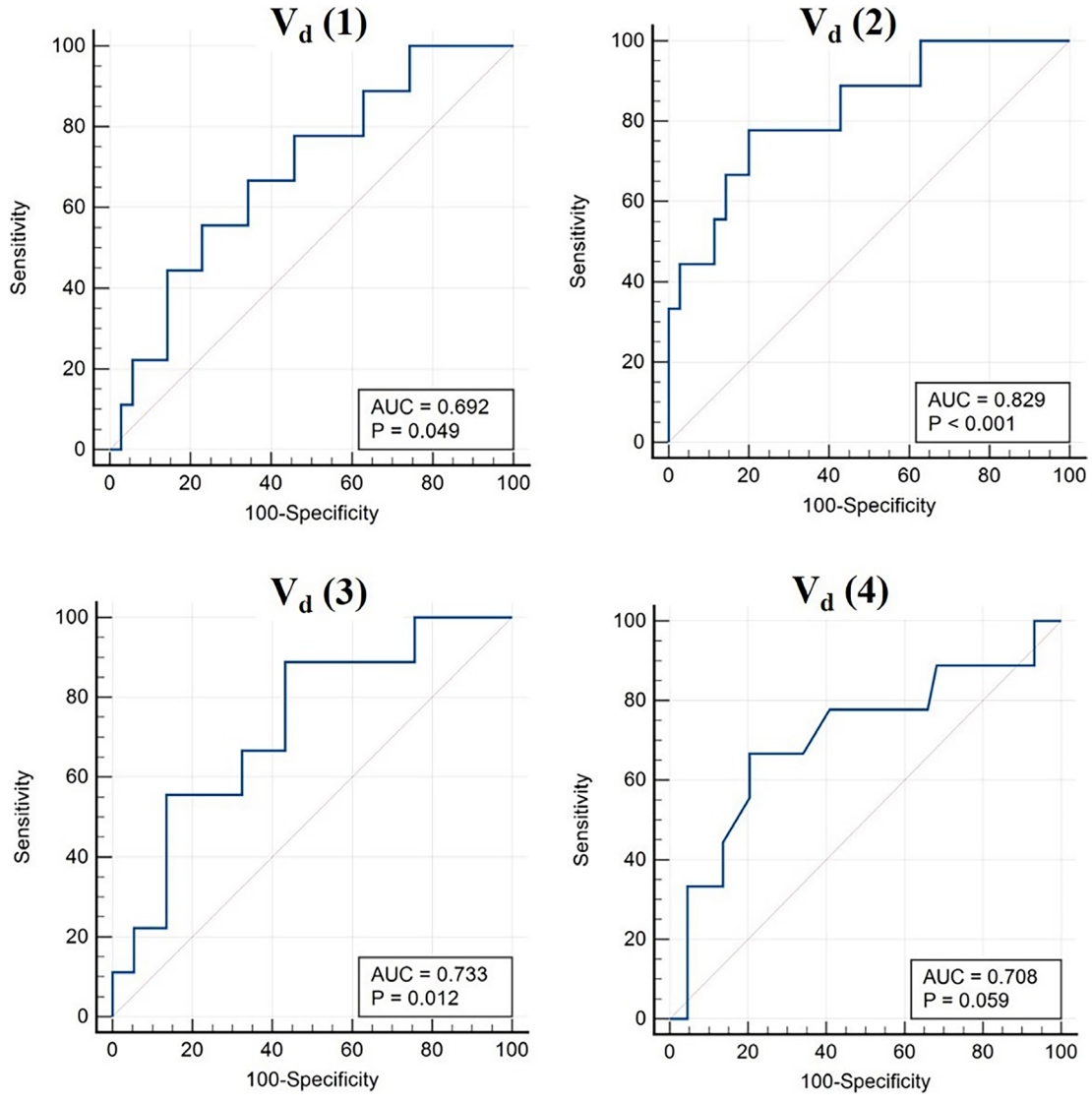

Figure S1. The area under the ROC curves of the volume of distributions (V_d (1), V_d (2), V_d (3), and V_d (4)) in the prediction of vancomycin-induced AKI.