Title: Evaluation of target area under the concentration-time curve of vancomycin in an initial dosing design: a single-center retrospective cohort study

Iida M[1, 2], Horita Y[1, 2, 3], Asaoka M[1, 2], Ohashi K[1, 3], Hirose T[4], Nomura Y[2], Kawahara M[4], Hotta Yuj[1, 2], Nakamura Atsushi[3], Furukawa-Hibi Yoko[1, 2]

[1]Department of Clinical Pharmaceutics, Graduate School of Medical Sciences, Nagoya City University, Aichi, Japan

[2]Department of Pharmacy, Nagoya City University Hospital, Aichi, Japan

[3]Division of Infection Prevention and Control, Nagoya City University Hospital, Aichi, Japan

[4]School of Pharmacy, Aichi Gakuin University, Aichi, Japan

Background: AUC-guided dosing of vancomycin was introduced in a clinical setting; however, the target range of non-steady-state AUCs, such as Day 1 AUC and Day 2 AUC, remains controversial. Therefore, we aimed to determine AUC thresholds and identify independent risk factors associated with acute kidney injury (AKI) to establish a safe initial dosing design for vancomycin administration.

Methods: We conducted a single-center, retrospective cohort study involving hospitalized patients who were treated with vancomycin at Nagoya City University Hospital between 1st April 2019 and 31th March 2023. Vancomycin-associated AKI was defined based on the modified Kidney Disease Improving Global Outcomes (KDIGO) criteria. Non-steady-state AUCs ($AUC_{0\text{-}24h}$, $AUC_{24\text{-}48h}$, and $AUC_{0\text{-}48h}$), were calculated according to the actual dosing schedule using the TDM software program SAKURA-TDM（Horita Y et al., TDM, 2023). The predictive performance of each threshold for AKI was evaluated using receiver operating characteristic curves. Univariate and multivariate logistic regression analyses were performed to identify potential risk factors for AKI.

Results: Of 456 patients selected from electronic medical records, 339 were included in this retrospective study. During the vancomycin treatment periods, 34 patients (10.0%) experienced AKI and 20 patients (5.9%) had an episode at the first sampling point (≤ 96 hours). The thresholds for predicting AKI were estimated as 456.6 mg·h/L for $AUC_{0\text{-}24h}$, 542.6 mg·h/L for $AUC_{24\text{-}48h}$, 945.7 mg·h/L for $AUC_{0\text{-}48h}$, and 14.0 μg/mL for measured trough levels, respectively. In a multivariate analysis, Day 2 AUC ≥ 542.6 mg·h/L (adjusted OR, 37.22; 95% CI, 9.81–203.63), piperacillin/tazobactam (adjusted OR, 8.35; 95% CI, 1.64–46.96), and vasopressors (adjusted OR, 5.51; 95% CI, 1.29–23.45) were identified as risk factors for AKI.

Conclusions: We identified AUC thresholds at the non-steady-state and trough levels at the first sampling points, which would be practically useful in the initial dosing design. Moreover, we constructed a predictive model for vancomycin-associated AKI, considering both the cutoff point of the Day 2 AUC and independent risk factors for AKI. Our results highlight the importance of monitoring not only the AUC but also trough levels during vancomycin treatment to reduce the likelihood of AKI.

Key Words: Vancomycin, AUC thresholds, AKI