Increased Vancomycin Clearance in Patients with Solid Malignancies

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INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to several antibiotics used widely and at high risk of causing infection in compromised patients, such as the elderly, immunosuppressed or postoperative patients and patients with catheters, including endotracheal intubation, trauma patients, premature infants and neonates. Vancomycin (VAN) is a glycopeptide antimicrobial agent that is the first choice for the treatment of MRSA infections. It has been previously reported that cancer patients exhibit a high rate of hospital-acquired MRSA, due to reduced immune function resulting from anticancer chemotherapy. It is worth noting that administration of VAN can lead to nephrotoxicity when the blood concentration of VAN immediately prior to administration is 20 µg/mL or more. Accordingly, when administering VAN, it is important to perform therapeutic drug monitoring (TDM) to assure effective and safe levels and to maintain a trough concentration of from 10 to 20 µg/mL. There are reports of VAN pharmacokinetics in MRSA-infected patients and population pharmacokinetic parameters in adult Japanese patients. An empirical Bayesian method has been applied to TDM data and the predictability of the Bayesian forecasting methods using population pharmacokinetic parameters of Japanese patients has been examined.

In recent years, a phenomenon called augmented renal clearance (ARC) has attracted attention, in which renal clearance increased. The mechanism of ARC is thought to result from elevated renal blood flow as a consequence of increased cardiac output. This can occur in systemic inflammatory response syndrome (SIRS) due to vasodilation following administration of vasoactive drugs and infusions. Among risk factors associated with ARC are sepsis, SIRS, surgery, and burn injuries. While a precise definition of ARC has yet to be made, several studies have shown that ARC is characterized by creatinine clearance (CLcr), ranging from >120 to >150 mL/min. VAN is primarily excreted in the urine, and its pharmacokinetic parameters vary depending on renal function. Recently, additional factors affecting VAN blood concentrations have been reported, including the fact that the presence or absence of cancer can affect VAN pharmacokinetics in children. In adult neutropenic patients administrated VAN, the distribution volume (Vdss) has been shown to increase and the elimination half-time (t1/2) to decrease. It has also been reported that VAN clearance (CLVAN) is significantly increased in elderly patients with malignant tumors, while the morbidity of underlying malignancy is not related.

VAN is often used in patients with suspected MRSA infections, regardless of the presence or absence of cancer, and this contributes greatly to the effectiveness of antibiotic therapy. However, overdoses of VAN can result in collateral renal dysfunction. In contrast, administration of VAN at inappropriately low doses increases the risks of generating bacteria that are resistant to VAN. In order to safely administer VAN in amounts that avoid production of resistant bacteria, it is important to monitor VAN blood concentrations. Previously, we have reported that hematological malignancy was a factor affecting CLVAN based on the results obtained by comparing VAN pharmacokinetic parameters in non-malignancy patients with hematological malignancy patients by means of multiple regression analysis using propensity score matchings. Unfortunately, for Japanese patients with solid malignancies, there are few large scale studies on VAN that provide phar-
macokinetic parameters, such as $CL_{VAN}$ and in small scale studies, confounding factors are not considered. In solid malignancies, the degree of confounding factors varies according to the stage. While being generally benign for healthy individuals in stage I, confounding factors become more complex for terminal stage cancer in stage IV. In order to clarify whether the pharmacokinetics of VAN is affected by cancer stage and whether the difference between stages affects VAN clearance, solid malignancies were divided into stages and analyzed. Herein, we performed a large scale investigation that specifically examines the effects that solid malignancies have on the pharmacokinetic parameters of VAN. Our study employs for the first time an empirical Bayesian method that utilizes multiple regression using propensity scores to adjust for confounding factors.

MATERIALS AND METHODS

Data and Characteristics of Patients This study was performed in accordance with the Declaration of Helsinki and its amendments, and was approved by the Ethics Committee of Tokyo Jikei University (Approved number: 30-213(9234)) and Hoshi University (Approved number: 30-026). The data were collected retrospectively from patients who were treated longer than 3 days with VAN following initial administration. VAN serum concentrations were measured during hospitalization from January 2015 to December 2018 in Jikei University Kashiwa Hospital (Chiba, Japan). Data from patients were excluded if they were under the age of 18 years, were renal replacement therapy patients or were patients with a change in serum creatinine (Scr) of $\geq 0.5 \text{mg/dL}$ or $\geq 50\%$ from the start time of VAN administration to time of blood VAN concentration measurement. All non-malignant tumor patients, who did not meet the exclusion criteria and who received VAN irrespective of medical department, were included in the control group.

General patient characteristics (sex, age, body weight and cancer type), laboratory test values (blood urea nitrogen (BUN), Scr, $CL_{cr}$, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin (T-Bil), direct bilirubin (D-Bil), $\gamma$-glutamyl transpeptidase ($\gamma$-GTP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), serum albumin (Alb), white blood cell (WBC), neutrophil (Neutro), C-reactive protein (CRP)), the dose and interval of VAN administration, and the trough blood concentration of VAN at steady state, had stomach cancer and 12 had pancreatic cancer (Table 1).

VAN serum concentrations were measured by a latex immunoturbidimetric assay using a Nanopia® TDM Vancomycin (SEKISUI MEDICAL, Tokyo, Japan). The VAN blood trough concentration value was taken after $\geq 3$ days following the start of administration. When data were more than one point, the last-measured value was used if the exclusion criteria were not met. When the VAN dose was changed in the middle of administration, the trough value measured before the dose change was used if it was after $\geq 3$ days from the start of administration, and if not, the trough value measured after $\geq 3$ days from the dose change was used.

Data Analysis Relationships were investigated among trough concentrations, dose, values of clinical laboratory tests, and other patient characteristics. Statistical comparisons were made between patients with solid malignancies and non-malignancy patients. $CL_{cr}$ was calculated by the method of Cockcroft–Gault. Using observed trough concentration data, an empirical Bayesian method was applied to obtain the individual estimated values of $CL_{VAN}$, $t_{1/2}$ and $V_{dss}$. Bayesian estimation was carried out for VAN using TDM analysis software Ver. 3.3 (Meiji Seika Pharma Co., Ltd., Tokyo, Japan) based on a linear two-compartment model. A population pharmacokinetic parameter set for Japanese adult patients was adopted as described previously.

Statistical Analysis Differences among patient characteristics, including VAN doses, observed trough concentrations, $CL_{VAN}$, $V_{dss}$, $t_{1/2}$, and values of clinical laboratory tests in patients with solid malignancy and non-malignancy patients, were statistically compared by the Mann–Whitney $U$ test or chi-square test. In addition, multiple regression analysis was performed on non-malignancy and solid malignancy patients using propensity scores. Logistic regression analysis was used to calculate the propensity scores. The propensity scores were calculated from BUN, Scr, $CL_{cr}$, AST, ALT, T-Bil, D-Bil, $\gamma$-GTP, ALP, LDH, Alb, WBC, Neutro and CRP. Factors contributing to $CL_{VAN}$ were then investigated using multiple regression analysis. The BUN, Scr, T-Bil, and D-Bil propensity score variables were selected as indicators of kidney function and the values of ALT, AST, $\gamma$-GTP, ALP, and LDH were taken as liver function index. The values for WBC, Neutro, and CRP were used as infectious disease indices. These were the most basic parameters that reflected the patient’s general condition and by which VAN clearance might be affected. All values for each variable are expressed as mean $\pm$ standard deviation (S.D.) unless otherwise indicated. A $p$-value of $< 0.05$ was considered statistically significant. Data analysis was performed using R software Ver. 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

General Patient Characteristics and Demographic Data Among the 990 patients who received VAN during the study period, 684 patients met the necessary criteria (Fig. 1). The 684 patients consisted of 261 non-malignancy patients, 162 solid malignancy patients and 261 hematological malignancy patients. Of 162 solid malignancy patients, 20 had pancreatic cancer; 20 had bile duct cancer; 15 had cervical cancer; 14 had stomach cancer and 12 had pancreatic cancer (Table 1). These could be further characterized as 50 (30.9%) for stage I and II; 98 (60.5%) for stages III and IV, and 14 (8.6%) for unknown. A summary of patient characteristics and demographic data for non-malignancy patients ($n = 261$) and solid malignancy patients ($n = 162$) used in this study are shown in Table 2.

VAN Dose and Observed Trough Concentration Summaries of VAN daily doses and observed trough concentrations are shown in Table 2. Among subject patients, the VAN daily dose was $28.1 \pm 11.2\text{mg/kg}$ in the non-malignancy group and $29.1 \pm 10.9\text{mg/kg}$ for ALL; $28.3 \pm 13.0$ for stage I, $28.8 \pm 9.3$ for stage II, $30.6 \pm 11.9$ for stage III, and $30.3 \pm 9.7\text{mg/kg}$ for stage IV in the solid malignancy group. The VAN trough concentrations were $11.8 \pm 5.7$ and $13.6 \pm 5.8$, $13.6 \pm 6.5$, $13.2 \pm 6.3$, $14.6 \pm 5.7$, or $12.5 \pm 5.2\text{µg/mL}$, respectively. Values of VAN daily dose or VAN trough concentrations were similar, not far apart, among groups and stages. While there were
These results suggest that a significant difference in the partial coefficient at every stage. The values were 0.001 for stage I, 0.049 for stage II, 0.049 ± 0.018 for stage III, or 0.053 ± 0.014 for stage IV in the solid malignancy group. The $t_{1/2}$ values were 37.1 ± 18.8 and 34.5 ± 15.9, 36.6 ± 11.9, 38.5 ± 25.2, 32.2 ± 10.0, or 34.3 ± 17.1 h, and the $V_{dss}$ values were 1.84 ± 0.62 and 1.79 ± 0.52, 1.90 ± 0.44, 1.85 ± 0.49, 1.76 ± 0.60, or 1.82 ± 0.49 L/kg, respectively. By univariate analysis, there were no significant differences in these pharmacokinetic parameters between the solid malignancy group in all and four stages and the non-malignancy group. These results indicate that the solid malignancies did not change the VAN parameters ($CL_{VAN}$, $t_{1/2}$, and $V_{dss}$) following univariate analysis.

Factors Contributing to $CL_{VAN}$ Values Since the $CL_{VAN}$, $t_{1/2}$, and $V_{dss}$ values pharmacokinetic parameters were not significantly different between the solid malignancy group and the non-malignancy group, multiple regression analysis was performed in both groups using propensity scores. As shown in Table 4, the partial regression coefficients were 0.137 for stage I (95% confidential interval (CI): 0.053 to 0.221, $p$-value = 0.002), 0.095 for stage II (95% CI: 0.028 to 0.163, $p$-value = 0.006), 0.071 for stage III (95% CI: 0.013 to 0.130, $p$-value = 0.018), 0.101 for stage IV (95% CI: 0.037 to 0.166, $p$-value = 0.002). In patients with solid malignancies, there was a significant difference in the partial coefficient at every stage. These results suggest that $CL_{VAN}$ is affected by the presence or absence of solid malignancies and that $CL_{VAN}$ values are increased in the solid malignancy patients as compared to the non-malignancy patients.

**DISCUSSION**

In the current study, factors contributing to VAN pharmacokinetic parameters were investigated. Values of $CL_{VAN}$ were 0.051 ± 0.019 L/h/kg for the non-malignancy group (261 patients) and 0.049 ± 0.016 L/h/kg for the solid malignancy group (All: 162 patients with different cancer types and stages)(Table 3). In addition, the $t_{1/2}$ values were 37.1 ± 18.8 and 34.5 ± 15.9h, and the $V_{dss}$ values were 1.84 ± 0.62 and 1.79 ± 0.52 L/kg, respectively. There were no significant differences in these pharmacokinetic parameters by univariate analysis. In addition, no significant difference was found in the analysis at each stage. However, multiple regression analysis under adjusting for propensity scores showed that the presence or absence of solid malignancies in each stage affected the $CL_{VAN}$ values (Table 4).

In order to confirm whether the pharmacokinetics of VAN varies depending on the stage of cancer, we have examined cancer type and number of cancer patients for each stage (Table 1) with reference to Table 2 contained in a report by Omote et al. Comparing these two tables, the number of cancer types and patients with solid malignant tumors were 32 types and 162 patients in our current study and 22 types and 65 patients in Omote’s report. The proportion of patients with solid malignancies at stages III and IV as compared to the number of target solid malignancies was 60% in this study and 51% in Omote’s report. The percentages of patients with solid malignancies at stages I and II were 30 and 15%, respectively. Despite the different populations, the clinical stages of the patients in both studies were primarily III and IV. The results of univariate analysis presented in this study (Table 3) were consistent with those of Omote et al., and the presence or absence of cancer did not affect VAN pharmacokinetics. However, a new multiple regression analysis in our current study revealed that the presence or absence of cancer affected VAN clearance.
Extensive studies are lacking comparing pharmacokinetic parameters of VAN in adult patients with solid malignant tumors relative to non-malignancy adult patients in Japan and overseas. In addition, as judging from the results of the trough concentrations in Table 2, where the average value is in the range of 10–15 $\mu$g/mL, it was evident that the dispersion is large. In particular, in the treatment of infectious diseases for which initial treatment is important, it is necessary that the blood concentration of VAN reach the therapeutic concentration range early. While the starting dose of VAN is also stated in the guidelines, an optimal starting dose for cancer patients has not been established. Regardless of being malignant patients or non-malignancy patients, it is difficult to determine the appropriate initial VAN dose to be administered.
using only Bayesian dosing design. In pediatric patients with malignant tumors, it has been reported that VAN doses higher than usual are required to reach expected blood concentrations. In addition, a previous report has shown that rats with osteosarcoma have increased total renal clearance of VAN. In contrast, Omote et al. have reported that there were no significant differences in CL\textsubscript{VAN} in Japanese patients with malignancies (hematologic and solid malignancies) as compared to non-malignancy patients. This result is consistent with our current results (Table 3). These authors concluded that CL\textsubscript{VAN} values in Japanese patients were affected by renal function, but not by the morbidity when considering 22 kinds of cancers (leukemia, lung, esophageal, bladder, lymphoma, etc.). However, these results were not adjusted to reflect confounding factors, including patient backgrounds. In our current study, we examined only solid malignant tumors as compared with non-malignancy patients. The severity of solid malignant tumors often varies greatly depending on stage. For example,
malignant tumors affects multiple regression analysis found that the presence of solid
regression coefficient, and this can be attributed to the small
II, III, and IV), a large variation was observed in the partial
contributed to the etiology of ARC. However, in all stages (I,
was found to be a factor affecting the presence or absence of
number of cases (Table 4). In our current study, we found
that the presence or absence of solid malignant tumors affects
CL\text{VAN}. One limitation of our study is that it was not possible
clearly identify these effects in the clinic in a way that
could suggest an appropriate starting VAN dose for admin-
istration to patients with solid malignancies. This limitation
arises out of being a retrospective study, and a prospective
study would be required to understand the details of VAN
pharmacokinetics.

As a result, since we have shown that solid malignant tu-
mors appear to increase CL\text{VAN}, administering higher VAN
doses to solid malignancy patients should be considered
relative to non-malignancy patients. In addition, when ad-
ministering VAN to patients with solid malignant tumors, it
is important to perform TDM from an early stage in order
to control blood VAN levels. It is generally thought in applying
TDM when administering VAN that initiation should be
performed earlier than usual in patients with solid malignant
tumors. It is important to consider the risk of underestimating
the trough concentration, since early TDM implementation
may be at a stage where the steady state has not been reached.
Particularly, if there is a possibility of increased VAN clear-
ance in patients with malignant tumors, blood concentration
should be evaluated at an early stage and then corrected to an
adjusted dose that provides appropriate treatment and achieves
adequate blood concentrations. In this way, treatment results
should be improved. The mechanisms by which ARC expres-
sion is induced by solid malignant tumors remains unclear,
and further studies are required.

CONCLUSION

We have shown that clinical monitoring VAN levels may be
particularly significant for patients with solid malignancies
to assure that appropriate intervention can be taken consistent
with efficient cancer treatment.

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