Clinical Efficacy of Therapeutic Drug Monitoring in Patients Receiving Vancomycin

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Efficacy of therapeutic drug monitoring (TDM) of vancomycin (VCM) was retrospectively investigated in 184 patients with methicillin-resistant Staphylococcus aureus (MRSA) infection. The incidence of nephrotoxicity was compared between the patients who received TDM practice (TDM group, n=73) and did not (non-TDM group, n=111). Creatinine clearance (CLcr) values decreased significantly after the VCM therapy in the non-TDM group (p<0.05). The patients with MRSA bacteremia or pneumonia were classified into two groups according to peak concentrations of VCM: above 25 μg/ml (Group A: n=29) and below (Group B: n=24). Mean duration of VCM therapy (14.1 d) in Group A was significantly shorter than that (27.0 d) in Group B. Mean cumulative total VCM doses (13.3 g) in Group A was significantly less than that (25.0 g) in Group B. These results indicate that monitoring peak concentration is essential to obtain better clinical effects for VCM therapy, and that the peak concentration above 25 μg/ml is more effective.

Key words vancomycin; therapeutic drug monitoring; nephrotoxicity; efficacy; methicillin-resistant Staphylococcus aureus (MRSA)

Vancomycin (VCM), a glycopeptide antibiotic, was developed and released in the 1950's for the treatment of aerobic gram-positive infections and has been widely used mainly in the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections. Early reports regarding the possibility of nephrotoxicity and ototoxicity led to concern about the use of VCM and monitor serum VCM concentrations.

In general, the purposes of therapeutic drug monitoring (TDM) are to improve clinical effects, to avoid side effects, and to reduce drug costs. In the case of VCM, however, an exhaustive review of the literature revealed that there are no studies analyzing a direct effect of serum VCM concentrations and clinical outcome.1—3) There have been a few studies examining the minimum inhibitory concentration (MIC)/minimum bactericidal concentration (MBC) ratios and cure rates,4—6) these studies are not efficient to answer the question what concentration of VCM was required for the successful treatment of infections. Recently, some clinical reports evaluating the TDM of VCM have proposed the following conclusions: 1) TDM is associated with a decreased incidence of VCM-induced nephrotoxicity, indicating that TDM is a cost-effective procedure,7—9) and 2) VCM works most effectively if the concentration at the site of infection is maintained above MIC values throughout the dose interval. So, the clinical efficacy of VCM can usually be obtained if the trough concentration is sufficiently above the MIC at the site of infected organisms.10,11)

Since the MIC values for susceptible organisms were below 5 μg/ml and reported toxicities had occurred most often at drug serum concentrations above 40 μg/ml, clinicians and researchers designated therapeutic trough concentrations at 5—15 μg/ml and peak concentrations at 25—40 μg/ml.1,12—14) In practice, however, the peak concentration hardly exceeds 40 μg/ml, as long as the trough concentration is kept below 15 μg/ml.15) For this reason, the policy of monitoring the trough concentration alone for VCM has recently spread worldwide. In Japan, however, both the trough and peak concentrations of VCM are monitored in most of hospitals. Therefore, it would be worthwhile to investigate whether monitoring peak concentration is essential or not.

The purpose of the present study was to investigate the clinical utility of the TDM VCM and the relationship between its peak concentrations and clinical effects in MRSA-infected patients.

MATERIALS AND METHODS

Subjects and Study Design Subjects (0—86 years of age) in this retrospective study were MRSA-infected patients who received intravenous infusion of VCM (Shionogi & Co., Ltd., Osaka, Japan) from January 1996 to March 2002 and also had confirmed the disappearance of the bacteria thereafter.

The incidence of nephrotoxicity, including VCM-induced or MRSA-related nephrotoxicity, was compared between the TDM group (n=73) and the non-TDM group (n=111). Serum VCM concentrations in the TDM group were monitored within 10 d from the start of VCM therapy. If VCM concentrations were monitored 10 d after the VCM therapy, those patients were not enrolled in either group. VCM doses were then adjusted to obtain both optimal trough concentrations (at 30 min before the dose) of 15 μg/ml and the peak concentrations (at 1 h after the end of infusion) of 40 μg/ml. The nephrotoxicity was evaluated by comparing a decrease in creatinine clearance (CLcr) values or an increase in serum creatinine (SCr) concentrations before and after the VCM therapy. The CLcr was estimated by using the Cockcroft–Gault equation. Patients who underwent surgical operation during VCM therapy or had more than 1.5 mg/dl of baseline SCr concentration were excluded from the study.

The TDM group received TDM practice according to physician’s instruction.

To investigate whether the TDM practice contributed in reducing the duration and doses of VCM therapy, pneumonia- or bacteremia-infected patients were extracted and compared between the TDM group (n=53) and the non-TDM group (n=46). The duration of the VCM treatment and cumulative total doses of VCM were compared between the two groups.

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The duration of the treatment was defined as a period from the first day (Day 1) of the VCM therapy to the day of MRSA disappearance at the infection sites. The cumulative total dose of VCM was defined as the dose given during this period. Both C-reactive protein (CRP) concentrations at Day 1 and minimum CRP concentrations measured within 14 d of Day 1 were also compared between the two groups.

To evaluate importance of the peak and trough concentrations of VCM, the subjects of the TDM group were classified into two groups according to the peak concentrations: TDM Group A, in which the peak concentrations were above 25 μg/ml (n=29), and TDM Group B, in which the concentrations were below 25 μg/ml (n=24). In these groups, the peak concentrations were determined within 10 d of Day 1. The relationship between serum VCM concentrations and the duration of the VCM therapy was then investigated between the two groups.

**VCM Measurement** Serum concentration of VCM was measured using a fluorescence polarization immunoassay method (TDx: Abbott Diagnostics, Chicago, IL, U.S.A.). This method has coefficients of variation of less than 6% for between-day and within-run imprecision. The lower limit of detection was 2.0 μg/ml. After centrifugation of blood samples, the serum was separated and preserved at 4 °C until sample analysis, which was performed within 4 h after sample collection.

**Statistical Analysis** All the data are given as mean±S.D. If the data of two different groups were compared for statistical analysis, an independent t-test (Welch's or Student's) was performed. We performed paired t-test to compare the CLcr values before and after the VCM therapy within the group. Spearman correlation analysis was also performed to investigate the relationship between serum VCM concentrations and duration of VCM therapy. A p value of <0.05 was considered to be statistically significant.

**RESULTS**

**Comparison of the Incidence of Nephrotoxicity between TDM and Non-TDM Groups** The incidence of nephrotoxicity was compared between the TDM group (n=73) and the non-TDM group (n=111), as shown in Table 1. Demographic characteristics of patients, i.e., gender distribution (male/female), their average ages, and initial CLcr values were similar in the two groups. The CLcr values decreased significantly during VCM therapy in the non-TDM group (p<0.05). The incidence rates for the increase of 0.3—0.5 mg/dl SCr were 4.1% and 7.2% in the TDM and non-TDM groups, respectively. The corresponding figures for an increase of 0.6—0.9 mg/dl SCr were 2.7% and 4.5%, respectively, and those for an increase of ≥1.0 mg/dl SCr were 1.4% and 6.3%, respectively, in the two groups.

**Changes in VCM Therapy-Related Parameters between TDM and Non-TDM Groups** The duration of VCM therapy, CRP concentrations, and cumulative total doses of VCM were then compared between the TDM and non-TDM groups (Table 2). The patient demographic characteristics, i.e., the total number of patients, their average ages, and the number of patients with either MRSA-infected pneumonia or bacteremia were confirmed as comparable in the two groups. No other antibiotics that are effective against MRSA (aminoglycosides, quinolones, minocycline or rifampicin) were administered. The CRP value of the TDM group was significantly higher than that in the non-TDM group at Day 1 (p<0.05). No significant differences in the duration of the therapy, the minimum CRP values and the cumulative total doses of VCM between the TDM and non-TDM groups were observed.

**The Relationship between Peak VCM Concentration and Other VCM Therapy-Related Parameters in the TDM Group** The relationship between the peak VCM concentration and its clinical effects were examined in the TDM Group A and Group B (Table 3). As a comparison, the patient demographic characteristics, the total number of patients, their average ages, and the number of patients with either MRSA-infected pneumonia or bacteremia, were confirmed as comparable in the two groups, as shown in Table 3. No significant difference was found in the initial CRP concentrations (at Day 1) between the two groups. The mean duration of VCM therapy in the Group A was 13 d shorter than those in the Group B (p<0.05). Mean cumulative total doses of VCM in the Group A were approximately 12 g less than those in the Group B (p<0.05). Minimum CRP concentrations measured within 14 d of Day 1 in the Group A were 1.8 μg/ml lower than those in the Group B (p<0.05).

![Figure 1](image_url) shows the relationship between the peak serum...
VCM concentrations and the logarithmic duration of VCM treatment in the TDM group (n = 53). Spearman correlation analysis showed a significant correlation between the peak concentrations and the duration of VCM treatment (r = 0.70, p < 0.001). The treatment duration varied widely among the patients having peak concentrations below 25 μg/ml. Some patients needed more than 30 d for the disappearance of the bacteria from the infection sites, while most of the patients whose peak concentrations were above 25 μg/ml needed less than 30 d for its disappearance of the bacteria. The relationship between the serum trough concentrations and the duration of VCM treatment was then examined in the TDM group (Fig. 2). Similar to the peak concentrations, the trough concentrations were significantly correlated to the logarithmic duration of VCM treatment (r = 0.51, p < 0.01). The durations of VCM treatment varied widely in the patients having the trough concentrations below 10 μg/ml.

DISCUSSION

The incidence of VCM-induced nephrotoxicity has been reported to occur in a range of 5 to 25%. 7,16–18) Similar results have been confirmed in the present study. That is, an increase in the baseline SCr concentration above 0.3 mg/dl occurred in 26 of 184 patients (14.1%): 6 of 73 (8.2%) and 20 of 111 patients (18.0%) in the TDM group and the non-TDM group, respectively (Table 1). The observed incidence of nephrotoxicity (8.2%) in patients of the TDM group was not higher than that in patients receiving other antibiotics such as β-lactam antibiotics. These results indicate that TDM practice could prevent the patients receiving VCM from nephrotoxicity.

The principles developed for pharmacokinetic and monitoring of aminoglycosides have been extrapolated to those for VCM because of presumed similarities in the toxicity profiles between VCM and aminoglycosides. However, the finding that the bactericidal action of VCM, i.e., a time-dependent killing manner, is quite different from that of the aminoglycosides, lets some practitioners to suggest that the necessity of measuring the peak concentration is doubtful in the TDM of VCM. 1,15,19,20) A study on the relationship between peak concentrations of VCM and the therapeutic response in the newborn infants with bacteremia showed that the median peak VCM concentrations were 27.4 μg/ml and 16.4 μg/ml in the patients with good and bad evolution, respectively. 21) However, these differences were not significant. In the present study, the duration of treatment for the TDM Group A, in which the peak VCM concentrations within 10 d of Day 1 were 25 μg/ml or above, was significantly shorter than that of the Group B, in which the peak concentrations were below 25 μg/ml. These results indicate that the clinical outcome in the patients with MRSA-infected pneumonia or bacteremia is improved by adjusting the peak VCM concentrations. This fact is also compatible with the present findings that the minimum CRP concentrations within 14 d of Day 1 were significantly lower than that of the Group B (Table 3).

The MIC90 of VCM for MRSA is usually 2 μg/ml or less 4–6) and its protein binding is approximately 50%. 11,22) The penetration percentage of VCM to lung tissue is at least 40%. 7,16–18) The penetration percentage of VCM to lung tissue is at least 20%. 23) These findings suggest that serum VCM concentrations above 20 μg/ml is necessary to achieve MIC90 of VCM in lung tissue for most MRSA-infected patients. In other words, it is important to obtain effective drug concentrations at the infection sites regardless of its action mechanism (i.e., concentration-dependent or time-dependent killing). From the present results, we have proposed that the peak VCM

![Fig. 1. Relationship between the Duration of VCM Therapy and the Peak Concentration.](image-url)

Blood samples for the peak concentration of VCM were drawn 1 h after the drip infusion at steady-state.

![Fig. 2. Relationship between the Duration of VCM Therapy and the Trough Concentration.](image-url)

Blood samples for the trough concentration of VCM was drawn 30 min before the drip infusion at steady-state.
concentration should be monitored to obtain a concentration above 25 µg/ml in the patients infected with MRSA-pneumonia or -bacteremia. In connection with the decrease of the infection period, total cumulative total doses of VCM in the TDM Group A was significantly less than those in the TDM Group B. This finding indicates that achievement of an adequate peak concentration also contributes to the cost-benefits of VCM therapy.

Some authors suggested that a lower limit for the trough VCM concentration is 5 µg/ml. On the other hand, Schaad et al. reported a relationship between successful care of 19/20 patients and bactericidal serum titers of 1:8 and concluded that serum VCM concentration of >12 µg/ml was necessary to achieve this titer ratio. Furthermore, in endocarditis, therapeutic failures have been reported with trough concentrations below 10 µg/ml. In the present study (Fig. 2), half of the patients having the trough concentrations of 5—10 µg/ml needed more than 30 d for the disappearance of the bacteria, whereas the patients having the trough concentrations above 10 µg/ml needed less than 30 d for their disappearance. The trough concentrations above 15 µg/ml, however, are considered to be more associated with an increased incidence of nephrotoxicity. These findings indicate that the trough VCM concentrations of 10—15 µg/ml are optimal for the MRSA treatment.

There was no significant difference in the duration of VCM therapy between the TDM and non-TDM groups (Table 2). Two reasons for this result could be proposed as follows. First, the TDM group might involve more patients with severe MRSA infections, when compared with the non-TDM group. This conjecture is based on the fact that significantly higher serum CRP concentrations were observed at the peak VCM concentration at an adequate level contributes to a decrease in the duration of the therapy.

In conclusion, TDM practice may prevent patients from developing nephrotoxicity during VCM therapy. Achieving the peak VCM concentration at an adequate level contributes to a decrease in the duration of the therapy.

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REFERENCES