Factors Affecting the Effect of Treatment of VCM Based on the Quantity of MRSA for Hospital-Acquired Pneumonia

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Abstract
Objective: To determine the factors affecting the antimicrobial effect of VCM on MRSA.
Study Design: Case series study.
Methods: This study was conducted on pneumonia patients admitted to a university-affiliated hospital between January 2000 and December 2008 and had MRSA in their sputum culture. From seven days prior to the starting VCM administration through the end of the administration, detailed information such as underlying diseases, VCM serum concentration and quantity of MRSA were recorded. Logistic regression analysis was carried out on current diseases, trough concentration, surgery experience, and the detection of Gram-negative bacteria to verify the antimicrobial effect of VCM.
Results: The number of subjects investigated this study was 55 subjects. Multiple logistic regression analysis did not yield any significant factors when carried out using the factors affecting the antimicrobial effect of VCM on MRSA as independent variables.
Conclusions: Multivariable analysis yielded no factors as being significant in affecting the antimicrobial effect of VCM, but did indicate in that patients aged 70 and older, the antimicrobial effect of VCM was poor for MRSA. This suggests that when pharmacists intervene in antimicrobial treatment for improved effects, it is important to consider not only the serum concentration of VCM, but also the background of the patient.

Key words: MRSA, vancomycin, pneumonia

Introduction

VCM (Vancomycin hydrochloride) is currently the most commonly used treatment for MRSA (Methicillin-resistant Staphylococcus aureus) pneumonia. The molecular weight of VCM is high while the biomembrane permeability is low, however, which leads to low transference to lung tissue, with concentration in the lungs being 1/3 to 1/5 of the VCM serum concentration.

In a prospective study, we experienced cases in which treatment had no effect even when the recommended serum VCM concentration was reached, and then gradual recovery occurred after confirming drug sensitivities and changing the antibiotic from VCM to SBT/ABPC (Sulbactam/Ampicillin), which is transferred more easily to the lungs. Reports suggested that it is difficult to show that VCM is adequately effective against MSSA (Methicillin-sensitive Staphylococcus aureus), as the antimicrobial effect of VCM have been proven to be inferior to penicillin for anti MSSA. Therefore, this indicated the significance of selecting antibiotic drugs based on an adequate understanding of bacterial susceptibility to drugs. Many hospitals practice TDM (therapeutic drug monitoring) to promote appropriate treatment, and there have been many reports that TDM practice has led to shorter periods of administration and a reduction in the total amount of VCM administered, contributing to the prevention of drug-resistant strains and reduced susceptibility to VCM in patients. In this prospective study, however, we experienced cases where the treatment was ineffective despite maintaining the recommended serum level. In the clinical conference of medical team, we also learned infection control doctor (ICD) takes into consideration blood flow abnormalities due to underlying diseases (e.g. arteriosclerotic disease, diabetes, and interstitial pneumonia) in antibiotic drug administration design. In this study, therefore, we set out to conduct a retrospective study utilizing a database for the purpose of studying the factors affecting the antimicrobial effect of VCM against MRSA, focusing on underlying diseases and maintaining optimal serum VCM concentration.
Methods

1. Duration and Institution

A retrospective study of patients infected with MRSA pneumonia was conducted at Osaka University Hospital from January 2000 to December 2008.

2. Study design and patient screening

A study was designed as a case series study. We selected patients admitted during the study period meeting the following conditions: 1) a diagnosis of MRSA pneumonia, 2) a laboratory test for cultures had been conducted, and 3) their serum VCM concentration had been measured. Subject data was extracted from a data warehouse, and of the extracted patients, we chose those whose electronic medical records indicated that bacteriological testing had detected MRSA in sputum culture, and whose CRP value was at least 0.3 mg/dL.

3. Study items

The study items included age, sex, underlying diseases, and surgery experience. Additionally, non-MRSA sputum culture, serum VCM concentration (trough value), and the quantity of MRSA were collected from the electronic medical records to examine subject background distribution.

4. Outcome evaluation

“The JRS Guidelines for the Management of Hospital-Acquired Pneumonia in Adults” by the Japanese Respiratory Society shows that the time of assessment of efficacy is within a week after the administration of antimicrobial agent\(^\text{3}\). To determine the antimicrobial effect of VCM on MRSA, data on MRSA status was collected within around one week after the start of VCM administration. Patients in which the quantity of MRSA decreased or disappeared one week after starting administration were designated the improvement group. Patients with no change in MRSA quantity one week after starting administration were designated the non-improvement group. The data for bacterial volume testing was represented in the electronic records as 1+ (10 to 99 colonies), 2+ (100 to 500 colonies), and 3+ (more than 500 colonies).

5. Statistical analysis

A basic comparison of age and sex was made between the improvement group and non-improvement group. Additionally, in order to study the factors affecting the antimicrobial effect of VCM against MRSA, logistic regression was carried out with underlying diseases, surgery experience, Gram-negative bacilli detection, and serum VCM concentration as independent variables. Conferences during the prospective study and consultation with the ICD were used as the basis for determining which underlying diseases affect antibiotic treatment. In this study, diabetes, cancer, interstitial lung disease and arteriosclerotic diseases (including angina, myocardial infarction, aortic dissection, arteriosclerosis obliterans, cerebral infarction, and cerebral hemorrhage, and so on) were defined as underlying diseases, and the presence of a diagnosis of any of these diseases prior to the VCM treatment was assessed. It was also reviewed whether patients had undergone surgery within the week prior to or following the VCM treatment. The Japanese Association for Infectious Diseases recommends that serum VCM concentration be kept between 10 and 15 µg/mL\(^\text{2}\). We compared two patient groups: one with a trough value of 10 µg/mL or higher, and the other with a trough value of less than 10 µg/mL. Since this study was retrospective, we measured value VCM serum concentrations in 2 or 3 days after administration were used. In cases where two measurements were made in one day, the lower value was used. The patients in the improvement group were assigned the value 1, and those in the non-improvement group were assigned the value 0. The classifications of dependent and independent variables are shown in Table 1. SPSS 11.5 J for Windows \(^\text{®}\) (Chicago IL) was used for the analysis, and a p value less than 0.05 was assumed to be statistically significant.

In addition, patient background before VCM administration, and the quantity of MRSA before and after VCM administration were compared for the improvement and non-improvement groups using a \(\chi^2\) test and a Student’s \(t\)-test.

Results

1. Subject background

The backgrounds of the 55 subjects in this study are shown in Table 2. The male to female ratio was 39:16, with a mean age of 59.8, the majority being seniors 60 years or older. Of the subjects, 15 patients had diabetes mellitus, 17 patients had cancer, 6 patients had interstitial lung disease, and 21 patients had arteriosclerotic disease. Thirteen patients had surgery one week prior to or following VCM administration, 41 patients were infected with Gram-
negative bacilli, and 20 patients maintained a serum VCM concentration level of 10 μg/mL or higher. The number of the improvement group was 21 patients. No significant differences were for age or sex found between the improvement and non-improvement groups (age: $p=0.31$, sex: $p=0.50$).

2. Factors affecting the antimicrobial effect of MRSA

Logistic regression analysis was conducted using the potential factors affecting the antimicrobial effect of VCM on MRSA as independent variables, and no significant results were found (Table 3). The comparison of two groups, one with a trough value of 10 μg/mL or higher, and the other with a value lower than 10 μg/mL, yielded no significant results for sex, age, or the factors deemed influential in this study (Table 4). A Student’s $t$-test was used on the average quantity of MRSA prior to and following VCM administration for the two groups, and no significant differences were found. Before the VCM administration, the ratio of quantity of MRSA was $<10\mu g/mL : \geq 10\mu g/mL = 1.6\pm 1.1 : 1.5\pm 1.2$ ($p=0.78$), and after administration, the ratio of quantity of MRSA was $<10\mu g/mL : \geq 10\mu g/mL = 1.3\pm 1.2 : 1.5\pm 1.1$ ($p=0.42$).

### Table 1 Data classification for logistic regression analysis

<table>
<thead>
<tr>
<th>Variables</th>
<th>1 (MRSA volume decreased or disappeared)</th>
<th>0 (Non-improvement)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dependent variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Diagnosed</td>
<td>No Diagnosed</td>
</tr>
<tr>
<td>Operation experience</td>
<td>Had operation within a week before or after treatment</td>
<td>Did not have operation within a week before or after treatment</td>
</tr>
<tr>
<td>Gram-negative bacilli in sputum culture</td>
<td>Infected</td>
<td>No Infected</td>
</tr>
<tr>
<td>Serum VCM concentration</td>
<td>$&lt;10\mu g/mL$</td>
<td>$\geq 10\mu g/mL$</td>
</tr>
</tbody>
</table>

### Table 2 Background of study patients (n=55)

<table>
<thead>
<tr>
<th>Variables</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [Average (S.D.)]</td>
<td>59.8 (17.9)</td>
</tr>
<tr>
<td>Sex (Female)</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15 (27.3)</td>
</tr>
<tr>
<td>Cancer</td>
<td>17 (30.9)</td>
</tr>
<tr>
<td>Interstitial lung disease</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td>Arteriosclerotic disease</td>
<td>21 (38.2)</td>
</tr>
<tr>
<td>Operation experience</td>
<td>13 (23.6)</td>
</tr>
<tr>
<td>Culture bacteria of sputum (Gram-negative bacilli)</td>
<td>41 (74.5)</td>
</tr>
<tr>
<td>VCM trough $\geq 10\mu g/mL$</td>
<td>20 (36.4)</td>
</tr>
</tbody>
</table>

### Discussion

In the multivariable analysis, no factors were found to be significant in the antimicrobial effect of VCM on MRSA. Conjecturing that this was due to the small number of samples, the distribution of each factor improvement and non-improvement groups was investigated. There were more patients with arteriosclerotic disease or interstitial pneumonia as underlying diseases in the non-improvement group. We inferred that the reason for this distribution was a reduced proportion of VCM reaching the lungs due to poor blood flow caused by arteriosclerosis combined with a low transference to the lung tissue, a characteristics of VCM. Interstitial lung disease results in inflammatory lesions on the alveolar wall were capillaries are present, so that when the pulmonary blood flow is low the VCM concentration in the alveoli is low, it is thought to affect the antimicrobial effect on MRSA. Our data showed that there has no significant difference of the average quantity of MRSA between before and after VCM administration in the group with a trough value of 10 μg/mL or higher (after : before $=1.5\pm 1.2 : 1.5\pm 1.1$). The result implied that VCM did not successfully work despite of enough trough value caused by poor blood flow.
In “The JRS Guidelines for the Management of Hospital-Acquired Pneumonia in Adults” by the Japanese Respiratory Society, the severity classification sets life prognosis factors as age 70 or higher for men and 75 or higher for women. Considering these criteria, we compared the improvement and non-improvement groups and found a significantly higher number of subjects aged 70 or higher in the non-improvement group (p=0.01) (Table 5), validating the JRS Guidelines. Behind this are a reduced blood flow to system-wide organs due to arteriosclerosis involved in aging, a reduced pulmonary blood due to potential pulmonary fibrosis, a reduced capacity to regenerate lung tissue after pneumonia, a weakened immune system, and other factors. Also, the prognosis for elderly patients with pneumonia is generally not good, confirming that adequate consideration of these age standards must be taken into account for VCM treatment.

The serum VCM concentration trough value was not a significant factor in the antimicrobial effect on MRSA. To validate this finding, a comparison was made between the
group with a trough value of 10 μg/mL or higher and the group with less than 10 μg/mL, looking at such factors as age, sex, diseases, surgery experience, Gram-negative bacterium culture, and the quantity of MRSA prior to and following VCM administration. No significant differences were found. Because the group with higher serum concentrations did not have a particularly higher quantity of MRSA, and it was not thought that the group had a high rate of serious diseases, it was judged that no bias was involved in arriving at this result. The reason for no significant findings for factors affecting the antimicrobial effect of VCM on MRSA is thought to be due to the small number of subjects and the variation in frequency of administration a day in the study. Although, it is important to maintain the appropriate serum concentration to prevent drug-resistant strains and mitigate adverse effects, and in the interest of favorable effects, the study also implies that an administration design which considers only the serum concentrations to be risky.

We assume that one of the reason why the improvement group were small (38%) in the study is assessing only bacterial volume. In assessing the effects of VCM, it is necessary to employ not only bacterial volume, but also comprehensive infection monitoring including body temperature, symptoms, sputum viscosity, and chest x-rays. Because this was a retrospective study, however, we acknowledge that the data had limitations in terms of the quantity and accuracy. Additionally, it is necessary to assess including MIC (minimum inhibitory concentration) to evaluate affect of VCM trough to the effects of VCM. In the future, prospective studies should be conducted with more cases, with analyses performed on an adequate amount of information, including sufficient laboratory data, severity of illness, imaging findings, and MIC.

**Conclusion**

Because neither the transitivity to lung nor antimicrobial effect on MRSA were adequate in general, special care should be taken when treating elderly nosocomial pneumonia patients with critical underlying diseases. To improve treatment, it is important to ascertain not only the serum concentrations of VCM and durations of treatment, but also the patient’s background and immune status, so that the transference of antimicrobial drugs to lungs, the risk for developing pneumonia, and the patient’s restorative capacity may be estimated. In the future, coordination with doctors at the bedside on intervening in antimicrobial treatment may be required of future pharmacists.

**References**


