Regular Article

Evaluation of Clinical Efficacy of Maeda’s Nomogram for Vancomycin Dosage Adjustment in Adult Japanese MRSA Pneumonia Patients

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Summary: The clinical efficacy of Maeda’s nomogram for vancomycin dosage adjustment was evaluated by comparison with a standard dosage regimen (package insert information: vancomycin dose reduced in elderly patients and patients with renal dysfunction, with Moellering’s nomogram used for renal-dysfunction patients) in adult Japanese MRSA pneumonia patients. Using Maeda’s nomogram, the vancomycin dose is fixed at 1,000 mg while the dosing interval is varied in accordance with individual creatinine clearance. Using a standard dosage regimen, 5 patients out of 27 (18.5%) achieved target plasma levels of vancomycin (25–40 mg/mL for peak and 5–15 mg/mL for trough) within 2–6 days. Using Maeda’s nomogram, 38 patients out of 53 (71.7%) achieved target levels in that time. A higher clinical response (complete resolution of all signs and symptoms of MRSA infection) to vancomycin therapy was also obtained with Maeda’s nomogram when evaluated approximately 2-weeks after discontinuation of vancomycin therapy (43.4% versus 18.5% for the standard regimen). In conclusion, the Maeda’s nomogram regimen with a 1,000 mg vancomycin dose was shown to achieve target plasma levels of vancomycin at a higher rate and provide higher clinical efficacy in vancomycin therapy of MRSA pneumonia patients, as compared with the currently available standard dosage regimen.

Key words: vancomycin; Maeda’s nomogram; dosage adjustment; MRSA pneumonia patients; TDM; bacteriological response

Introduction

The glycopeptide antibiotic vancomycin has been widely used in the treatment of gram-positive infectious diseases; especially those caused by methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant Staphylococcus epidermidis (MRSE). This antibiotic, especially in concomitant use with other antibiotics, induces nephrotoxicity and ototoxicity as side effects, though recent incident rates with today’s pure drug formulation are less common or less severe than originally reported.¹⁻³ In vancomycin therapy, plasma levels of vancomycin are monitored to avoid side effects and obtain effective clinical responses in each individual. The desired target peak and trough levels of vancomycin vary among medical institutions and the need for dose reappraisal and monitoring has been reported.³⁻⁵ The plasma clearance of vancomycin is regulated primarily by glomerular filtration; therefore, renal dysfunction modifies such pharmacokinetics as plasma disappearance or higher trough levels. According to the package insert (Vancomycin Hydrochloride®, Shionogi Co., Ltd., Osaka, Japan), the vancomycin dosage regimen for adult patients with normal renal function is 1 g every 12 h or 0.5 g every 6 h, and the vancomycin is administered by intravenous infusion over the course of more than 1 h. In elderly patients, the dose of vancomycin and dosing interval are reduced to 0.5 g every 12 h or 1 g every 24 h, respectively. For patients with a low creatinine clearance (CLcr), the daily vancomycin dose (mg) is calculated with Moellering’s nomogram as a function of CLcr (mL/min) estimated by the method of Cockcroft-Gault.⁶⁻⁷ Several methods have been proposed for setting the initial dosage

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regimen of vancomycin therapy, including Moellering’s nomogram,\textsuperscript{6} Matzke’s nomogram,\textsuperscript{3} the population mean method\textsuperscript{9} and the Bayesian method.\textsuperscript{10,11}

Previously, we proposed a simple nomogram, or Maeda’s nomogram, for setting the initial dosage regimen in vancomycin therapy. Maeda’s nomogram fixes the vancomycin dose at 1,000 mg and varies the dosing interval based on individual CLCr values.\textsuperscript{12} The present clinical trials were carried out to evaluate the clinical efficacy of Maeda’s nomogram by comparing the therapeutic drug monitoring (TDM) data and clinical responses obtained with those obtained using a standard dosage regimen in adult Japanese MRSA pneumonia patients.

**Methods**

**Standard dosage regimen and Maeda’s nomogram regimen:** The standard dosage regimen was that found in the vancomycin package insert (Vancomycin Hydrochloride®, Shionogi Co., Ltd., Osaka, Japan). Using this dosage regimen, adult patients with normal renal function receive 1 g every 12 h or 0.5 g every 6 h. Elderly patients (>70 years old) receive 0.5 g every 12 h or 1 g every 24 h. For patients with a low creatinine clearance (CLCr, less than 70 mL/min), the daily vancomycin dose (mg) is calculated with Moellering’s nomogram\textsuperscript{6} and administered at 8, 12, or 24 h interval. Patients receive vancomycin by intravenous infusion lasting more than 1 h.

Maeda’s nomogram\textsuperscript{12} sets the dosing interval (days) in relation to individual CLCr (mL/min), with vancomycin dose fixed at 1,000 mg and CLCr estimated using the nomogram (Fig. 1). In constructing the nomogram, Moellering’s nomogram\textsuperscript{6} was utilized to estimate daily dosage as follows: daily dose (mg) = CLCr (mL/min) × 15.4, where CLCr is estimated by Nielsen’s nomogram\textsuperscript{13} using body weight, age, sex and serum creatinine level. The dosing interval (days) is then adjusted by dividing 1,000 mg by the estimated daily vancomycin dose (mg). Patients receive the vancomycin by intravenous infusion lasting more than 1 h.

**Patient characteristics:** Between June 2001 and May 2005, vancomycin therapy and monitoring of plasma levels were performed in 80 (58 male, 22 female) adult MRSA pneumonia patients at Chugoku Rousai General Hospital and Okayama Rousai General Hospital. A standard dosage regimen of vancomycin was administered to 27 MRSA patients (20 male, 7 female, 74.5 ± 16.7 [20–95] years old, 54.5 ± 9.9 kg body weight, serum creatinine 0.85 ± 0.56 mg/dL). Maeda’s nomogram was applied in determining dosage regimens for 53 MRSA patients (38 male, 15 female, 78.2 ± 9.0 [52–91] years old, 54.0 ± 9.9 kg body weight, serum creatinine 0.90 ± 0.40 mg/dL). There were no significant differences in patient parameters between the two groups (standard dosage group versus Maeda’s nomogram group).

**TDM data and clinical efficacy:** The Hospital Ethics Committee approved the clinical trials of Maeda’s nomogram. Informed consent was obtained from each patient. The clinical efficacies of these 2 dosage regimens were evaluated from vancomycin TDM data obtained within 2–6 days of vancomycin administration and clinical therapeutic (bacteriological) responses in MRSA patients obtained after discontinuation of vancomycin treatment. Peak plasma levels, or the level 1 h after the end of infusion, and trough plasma levels of vancomycin were obtained for each patient. When target vancomycin levels (25–40 µg/mL for peak and 5–15 µg/mL for trough)\textsuperscript{14} were not achieved within 7 days on either dosage regimen, the dosage regimen was altered to the Bayesian method.\textsuperscript{10} Patients shifted to the Bayesian method were omitted from the analysis of results in the present study.

The clinical therapeutic responses of patients to
vancomycin therapy were evaluated by measuring serum concentration of C-reactive protein (CRP), white blood cells (WBC), fever, and by culturing sputum samples to detect MRSA. Cultures were repeated every 3 days, if clinically indicated, and on the last day of treatment and the 4th day after discontinuation. Clinical outcomes, evaluated approximately 2 weeks after discontinuation of treatment, were categorized as follows: cure (complete resolution of all signs and symptoms of MRSA infection); improvement (resolution or no progression in most signs and symptoms); or failure (persistence or progression in all signs and symptoms on the 5th day of therapy). Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dL or 50%, whichever was greater, on 2 consecutive occasions any time during vancomycin therapy.

**Analysis:** Plasma vancomycin levels were measured by fluorescence polarization immunoassay (TDX; Abbott Laboratories, North Chicago). Serum concentrations of CRP and creatinine were determined by latex photometric immunoassay (LPIA) and creatinase-sarcosine oxidase-peroxidase, respectively. Data were expressed as the mean and standard deviation. The criterion for statistical significance was a P value of less than 0.05, which was estimated by a $x^2$-test and non-paired Student’s t-test.

**Results**

**TDM data:** A standard dosage regimen of vancomycin was administered to 27 MRSA patients and Maeda’s nomogram regimen to 53 patients. As shown in Table 1, for the standard dosage regimen, seven different dosage modalities were used among 27 patients depending on their CLcr values. With the Maeda’s nomogram regimen, the vancomycin dose was fixed at 1,000 mg while only dosing interval was varied, resulting in 4 different dosage modalities among 53 patients. Early stage TDM data are shown in Figs. 2 and 3. Using

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**Table 1.** Variation in vancomycin dose and dosing interval among patients according to Maeda’s nomogram and standard dosage regimens, and the number of adult Japanese MRSA patients participating.

<table>
<thead>
<tr>
<th>Vancomycin dose (mg)</th>
<th>Dosing interval (hr)</th>
<th>Standard method (No. of patients)</th>
<th>Maeda’s method (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 12</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>500 8</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>500 12</td>
<td></td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>750 12</td>
<td></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1000 12</td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1000 24</td>
<td></td>
<td>10</td>
<td>32</td>
</tr>
<tr>
<td>1000 48</td>
<td></td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>1000 72</td>
<td></td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Maeda’s nomogram regimen was applied to 53 patients and a standard dosage regimen was applied to 27 patients.
Fig. 3. Plasma vancomycin trough levels plotted against peak levels observed in vancomycin therapy based on Maeda's nomogram regimen in 53 Japanese adult MRSA patients.

Table 2. Pharmacokinetic data and clinical efficacy of standard dosage and Maeda's nomogram regimens in adult Japanese MRSA patients

<table>
<thead>
<tr>
<th></th>
<th>Standard method</th>
<th>Maeda's method</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>27</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Peak level (µg/mL)</td>
<td>31.2 ± 11.9</td>
<td>31.9 ± 6.5</td>
<td>0.735</td>
</tr>
<tr>
<td>Trough level (µg/mL)</td>
<td>13.0 ± 9.2</td>
<td>9.4 ± 4.2</td>
<td>0.016</td>
</tr>
<tr>
<td>Therapeutic range (%)</td>
<td>18.5</td>
<td>71.7</td>
<td>6.46×10⁻³</td>
</tr>
<tr>
<td>AUC₀₋₂₄ (µg hr/mL)</td>
<td>530.7 ± 232.8</td>
<td>494.8 ± 108.5</td>
<td>0.318</td>
</tr>
<tr>
<td>Treatment period (day)</td>
<td>11.6 ± 5.0</td>
<td>11.4 ± 5.4</td>
<td>0.993</td>
</tr>
<tr>
<td>Cumulative dose (g)</td>
<td>12.6 ± 6.5</td>
<td>9.1 ± 4.3</td>
<td>1.86×10⁻³</td>
</tr>
</tbody>
</table>

Clinical response
- Cure (%) 18.5 43.4 0.027
- Improvement (%) 59.3 45.3 0.237
- Failure (%) 22.2 11.3 0.197

Microbiologic response
- Eradication (%) 7.4 20.0 0.451

Nephrotoxicity (%) 14.8 3.8 0.086

Statistical significance was estimated by an χ²-test or non-paired Student’s t-test.

The standard dosage regimen, only 5 patients out of 27 (18.5%) reached the desired target plasma level of vancomycin (Fig. 2). Using the Maeda’s nomogram regimen, 38 patients out of 53 (71.7%) reached the desired target level (Fig. 3). Thus, the simple Maeda’s nomogram method was found to achieve target plasma levels at a significantly higher rate than the currently available standard method (P<0.05).

Clinical therapeutic responses in adult MRSA patients: The clinical therapeutic responses to vancomycin therapy in MRSA patients, evaluated approximately 2 weeks after discontinuation of treatment, are summarized in Table 2. With the standard dosage regimen, cures were observed in 5 patients out of 27 (18.5%), while 6 patients (22.2% of patients) were classified as treatment failures. With Maeda’s nomogram regimen, cures were observed in 23 patients out of 53 (43.4%), and, again, 6 patients (11.3%) were treatment failures. Thus, the simple Maeda’s nomogram regimen showed significantly higher clinical efficacy than the standard dosage regimen (P<0.05), analyzed by a χ²-test using 2×2 contingency table [cure and others (improvement + failure)]. No differences were found between the 2 groups with respect to microbiologic response and nephrotoxicity.
Table 3. Clinical efficacy of standard dosage versus Maeda’s nomogram regimens in relation to plasma vancomycin levels in adult Japanese MRSA patients

<table>
<thead>
<tr>
<th>Target level of vancomycin</th>
<th>Standard dosage regimen</th>
<th>Maeda’s nomogram regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cure</td>
<td>Improvement</td>
</tr>
<tr>
<td>Peak + Trough</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Trough only</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Peak only</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Outer</td>
<td>2</td>
<td>5</td>
</tr>
</tbody>
</table>

Each value represents patient number. Maeda's nomogram regimen was applied to 53 patients and a standard dosage regimen was applied to 27 patients. Target levels of plasma vancomycin were 25–40 μg/mL for peak and 5–15 μg/mL for trough. Outer: serum vancomycin levels were <25 or >40 μg/mL for peak and/or <5 or >15 μg/mL for trough.

Discussion

Previously, we analyzed retrospectively vancomycin TDM data obtained using a standard dosage regimen in 99 adult Japanese MRSA patients.12 Of those patients, 65 received vancomycin at a dose of more than 1,000 mg (at 12 h, 24 h or 48 h intervals) and 35 patients (54%) reached the desired target vancomycin range after several administrations. In contrast, only 2 patients out of 34 (5.9%) reached the target vancomycin range when they received a dose of less than 750 mg (750 mg, 2 patients and 500 mg, 32 patients). This fact suggested that a vancomycin dose greater than 1,000 mg was required in adult patients, irrespective of renal dysfunction, to achieve therapeutic peak vancomycin levels in the early stage of vancomycin therapy. In Matzke’s method,9 the initial dose of vancomycin is higher, irrespective of the patient’s renal dysfunction, although this method is difficult to follow precisely in clinical trials. In addition, it is suggested that exposure time at a level greater than MIC and the time required to reach a level greater than MIC are important factors clinically.17,18 Recently, it is generally accepted that higher calculated area under the inhibitory concentration-time curve (AUC24/MIC, or AUIC) for vancomycin in plasma is important in vancomycin therapy, indicating that a higher initial dose of vancomycin, which leads to a higher AUC24, can achieve a higher clinical efficacy.19-21 Based on these considerations, in Maeda’s nomogram, the vancomycin dose was fixed at 1,000 mg even for patients with impaired renal function, while the dosing interval was varied depending on individual CLcr (Fig. 1). Previously, we examined Maeda’s nomogram in 6 adult MRSA patients and found that 4 patients (67%) achieved the therapeutic range of vancomycin in the early stage of therapy.12 In the present study, we re-evaluated the clinical efficacy of Maeda’s nomogram regimen by increasing patient numbers and by comparing TDM data and clinical therapeutic responses with those obtained using a currently available standard dosage regimen. With Maeda’s nomogram method, 4 different dosage modalities were required for 53 MRSA patients depending on their renal function (ratio of modalities/patients number = 0.075) (Table 1). In contrast, 7 dosage modalities were required for the 27 MRSA patients receiving a standard dosage regimen (ratio of modalities/patients number = 0.259). As shown in Figs. 2 and 3, Maeda’s nomogram method achieved the therapeutic range of vancomycin levels at a significantly higher rate than the standard dosage method (71.7% versus 18.5%). In addition, in the present study, 45 patients were initially enrolled in the standard dosage group and 57 patients in the Maeda’s nomogram group. However, patients decreased to 27 from 45 in the standard dosage group due to inadequate dosage adjustment. In contrast, only 4 patients shifted to the Bayesian method among 57 in the Maeda’s nomogram group. All these facts suggest that dosage adjustment with Maeda’s nomogram is far simpler and easier than the standard dosage adjustment.

In the present study, the clinical efficacy of each dosage regimen was evaluated in relation to their plasma vancomycin levels (Table 3). With the standard dosage regimen, no clear correlation was found between clinical efficacy and plasma vancomycin levels. With Maeda’s nomogram regimen, cures were usually observed in patients that had achieved target peak and trough levels of vancomycin. In addition, Maeda’s nomogram method showed higher therapeutic responses in the treatment of MRSA, though analysis by a x²-test using 2 x 3 contingency table (cure-improvement-failure) did not reach statistical significance (Table 2). Our data may support the suggestion that achieving higher AUIC of plasma vancomycin in the early stage of vancomycin therapy leads to higher clinical efficacy, as reported previously.19-21 Recently, Teramachi et al.20 evaluated retrospectively the clinical efficacies of Moellering’s method, Marzke’s method, Maeda’s method, and the population mean method, using vancomycin TDM data obtained in 72 adult MRSA patients. They reported that Maeda’s method achieved the therapeutic range more frequently.
than the other 3 methods, and that the Bayesian focusing technique was valuable in correcting the vancomycin dosage regimen more precisely. Collectively, our previous report, the present report, and the reports by Teramachi et al. and Nagano et al. demonstrate the clinical usefulness of Maeda’s method in setting the initial dosage regimen in vancomycin therapy for adult MRSA patients. Several methods are available to estimate individual CLcr including Nielsen’s nomogram, Cockcroft and Gault’s method, and direct estimation of CLcr using urinary excretion rate of creatinine and serum creatinine level in patients. Any reliable CLcr values can be used to calculate dosing intervals for Maeda’s nomogram.

In conclusion, Maeda’s nomogram regimen, consisting of a fixed vancomycin dose (1,000 mg) and varied dosing intervals depending on individual renal function, was found to achieve desired plasma levels of vancomycin at a higher rate and provide higher clinical efficacy in vancomycin therapy compared with the currently available standard dosage regimen.

References
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