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Abstract

Teicoplanin has a long serum half-life, and therefore it takes time to reach a steady-state concentration. An initial loading procedure has been recommended for teicoplanin to enable prompt reaching of the optimal serum trough level (10-15 μg/ml). However, the dose of teicoplanin that should be administered to patients with varying renal function levels remains inconclusive. In this study, we monitored the serum concentrations of teicoplanin in the patients with methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and compared different teicoplanin serum concentrations and their clinical efficacy, investigating the significance of the mean dose administered during the initial 3 days. The study included 48 patients with MRSA pneumonia. The peak and trough concentrations of teicoplanin were determined utilizing a fluorescence polarization immunoassay and a two-compartment Bayesian population model. Teicoplanin was given at a loading dose of 400 or 800 mg on the first day, followed by maintenance doses of 200 or 400 mg. The mean initial dose (MID) over the first 3 days was calculated as (loading dose + dose for 2nd day + dose for 3rd day) / 3. Patients with MID of 266.7 mg or less (400mg for loading, 200mg over the 2nd and 3rd day) did not have a trough level that exceeded 10 μg/ml at the point before the injection on the 4th day. Even in patients with hemodialysis (HD), an MID of 266.7

mg was not enough to provide a trough level of 10 μ g/ml. Patients with an MID than 533.3mg had significantly elevated trough levels, showing better outcomes. A multiple regression formula for predicting trough level before the fourth day of administration is given as: 0.034 + 0.030 x (MID, mg) - 0.057 x creatinine clearance (Ccr; ml/min). These findings suggest that 800 mg as an initial dose, followed by 400 mg maintenance doses over the following 2 days, makes it possible to safely attain an optimal trough level, even in the patients with HD.

Key words: Therapeutic drug monitoring, Teicoplanin, Loading dose, MRSA

Introduction

The glycopeptide antibiotics, vancomycin and teicoplanin are being used in Japan only for patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections, while they are widely employed in other countries for gram-positive strain infections, in particular for severe or multi drug-resistant infections. Teicoplanin possesses characteristic advantages over vancomycin such as its prolonged serum half-life, its postantibiotic effect, and a lower frequency of nephrotoxicity or red man syndrome 1). However, teicoplanin needs a loading dose to enable a prompt rise in serum concentration, but the optimal loading dose is not known. In this context, we undertook a retrospective study, monitoring teicoplanin serum concentrations, comparing the results with different concentrations for efficacy and toxicity.

Patients and Methods

Subjects

Serum and sputum samples and chest radiographs were obtained for 48 consecutive patients (mean age, 74.3±11.5 years; 38 men and 10 women) who were given a diagnosis of MRSA pneumonia. The diagnosis was based on all the following findings: fever over 37.5 ℃, cough, purulent sputum, significantly positive cultures of

MRSA in the sputum, an image of the *Staphylococcus* englobed in the Gram's stain of expectorated mucus, newly developed infiltrative shadows on chest X-ray films, leukocyte counts beyond 8,000/μl, and positive for C-reactive protein (CRP) or elevation of erythrocyte sedimentation rate (ESR). Subjects with suspected mixed infections were excluded from the study. Of the 48 patients, 6 patients were receiving hemodialysis (HD).

Measurement of teicoplanin concentration in serum

Following the recommended regimen that is used in Japan, a loading dose of 200 - 400 mg of teicoplanin, twice a day, was adminitstered to the patient on the first day, and then teicoplanin for maintenance was given once a day at a dose of 200-400 mg. No other antimicrobials were used during the study. In this study, blood samples were taken at the following three points: (i) just before the injection on the 4th day, (ii) 2h after the administration on the 4th day, and (iii) just before the treatment on the 5th day. These points correspond to the trough level on the 4th day (Cpre), the peak level on the 4th day (C1), and the trough level on the 5th day (C2), respectively.

The serum concentrations of teicoplanin were determined by utilizing a fluorescence polarization immunoassay, and then the dose to be administered was

designed so as to obtain a planned trough teicoplanin serum level of 15 μg/ml , after estimating the volume of distribution (Vd) and the elimination constant (Kel), employing a two-compartment Bayesian population model 2). The effect of teicoplanin was evaluated in terms of the clinical findings, laboratory data, and bacteriologic responses. The classifications used were as follows: “excellent” for subjects with eradication of MRSA and improvement of clinical data, leukocyte counts, CRP, ESR, and infiltrative shadows on chest X-ray films; “good” for subjects with decreased MRSA and improvement of clinical data, leukocyte counts, CRP, ESR, and infiltrative shadows on chest X-ray films; and “poor” for subjects with persistent MRSA or no improvement in one of the following parameters: clinical data, leukocyte counts, CRP, ESR, or chest X-ray findings.

Creatinine clearance (Ccr, ml/min) in adult males was calculated according to the formula of Cockcroft and Gault 3):

Ccr = (140-age) x (weight in kg) / 72 x (serum creatinine (mg/dl)) (15% less in females).

A significant change in laboratory data was defined as an increase of 120% or more from an upper limit of the normal range when data were normal before therapy or an increase of 200% or more from an abnormal data level before therapy.

Statistical analysis

Data values are presented as means ± SD. One-way analysis of variance was used when multiple comparisons were made. Differences among groups were considered significant when *P* was less than 0.05.

Results

Forty-eight patients were available for the retrospective analysis. Figure 1 shows the relationship between the clinical efficacy, patients' ages, and serum trough levels of teicoplanin before the 4th day administration. The mean trough levels were; 7.9 ± 4.7 μg/ml in subjects with excellent responses; 8.2 ± 4.7 μg/ml in those with good responses; 6.5 ± 3.0 μg/ml in those with poor responses. No subject had a trough level over 20 μg/ml. Twenty-two (45.8%) subjects had an excellent response; 14 (29.2%) had a good response, and 12 (25.0%) had a poor response. Subjects with a poor response had the lowest mean trough level. Differences in trough levels between age groups (patients aged < 65 years, patients aged > 65 and < 80, and patients aged ≧ 80 years) were not significant.

Figure 2 shows the administered doses of teicoplanin and trough levels in six

patients suffering from renal dysfunction. In cases 1, 2, 3, and 4 who had a loading dose of 400 mg, followed by 200 mg, the trough levels (before the injection on the 3rd day in case 1 and before the injection on the 4th day in case 2, 3, and 4) were 7.0 μg/ml, 6.5 μg/ml, 4.6 μg/ml, and 3.6 μg/ml, respectively. Hence, it seemed that even in subjects with renal dysfunction, a loading dose of 400 mg followed by a maintenance dose of 200 mg were not enough to attain the recommended trough level of 10 to 15 μg/ml. In contrast, as seen in case 5, who received an initial dose of 800 mg, and then 400 mg on the 2nd and 3rd days, the trough level before the 4th day reached 18.2 μg/ml. Case 6, who was treated for 7 days with 200 mg of teicoplanin daily, had an appropriate trough level. In case 2, the serum concentrations of teicoplanin before and after HD were 5.6 μg/ml and 4.9 μg/ml, and elimination by HD seemed to be minimal, as has been reported by others 4)5).

These findings raised the question as to whether the loading dose of 400 mg and the successive maintenance dose of 200 mg might be insufficient. Thus, we focused on the relationship between the mean dose for the first 3 days (mean initial dose: MID), and the trough level before the 4th day. The MID was calculated as follows: (loading dose + dose on 2nd day + dose on 3rd day) / 3. In most subjects, the MIDs were given as (400 + 200 + 200) / 3 = 266.7 mg or (800 + 400 + 400) / 3 = 533.3 mg.

The mean MIDs were 359.4mg in those with excellent responses, 337.8mg in those with good responses, and 297.0mg in those with poor responses.

As illustrated in Fig.3, the trough levels at the point before the 4th day of administration (Cpre) in the 48 patients were closely correlated with a higher MID (r=0.7157). In all but 1 of the patients with MID of 266.7 mg or less, the trough level before the 4th day did not exceed 10 μ g/ml. On the other hand, most patients with an MID higher than 533.3 mg showed significantly elevated trough levels (p=0.0003). With respect to the clinical outcome, patients with trough levels (Cpre) lower than 10 μ g/ml tended to have poor outcomes.

To investigate the influence of renal function on the trough levels before the 4th day administration (Cpre), we compared the relation between the trough levels, Ccr, and the MID (Fig.4). The Ccr data were obtained from 40 patients. In patients with the same range of MID, those with a higher Ccr tended to show lower trough levels. No dependence of trough levels on the presence or absence of HD was recognized (Fig.4). A multiple regression analysis formula for predicting trough level before the 4th day of administration is given as: 0.034 + 0.030 x MID (mg) -0.057 x Ccr (ml/min).

Table1 Incidence of abnormal laboratory data

	(cases)	Crt	BUN	AST or ALT or ALP	Plts	total dose (g)
total cases	(48)	4.2% (2)	8.3% (4)	20.8% (10)	2.1% (1)	4.89 ± 3.90
non-HD	(42)	4.8% (2)	9.5 % (4)	21.4% (9)	0.0% (0)	5.06 ± 3.99
HD	(6)	0.0% (0)	0.0% (0)	16.7% (1)	16.7% (1)	3.53 ± 3.04

Table 1 summarizes the incidence of abnormal laboratory data in the 48 patients. Elevation of creatinine (Crt) and blood urea nitrogen (BUN) was observed in 2 (4.2%) and 4 patients (8.3%), respectively. Ten patients (20.8%) had an elevation of aspartate aminotransferase (AST), or alanine aminotransferase (ALT), or alkaline phosphatase (ALP). No significant differences in the frequencies of abnormal laboratory data were noted between patients with and without HD. No association between the total doses used and the incidence of abnormal data was found (data not shown). No major complications were observed in any patient.

The intensification of the initial dose was found to cause an increase in the trough level before the 4th day (Cpre) , thereby possibly resulting in a good outcome, as seen in Fig. 3, although this intensification could possibly lead to a higher frequency of abnormal laboratory findings or adverse reactions. In this regard, however, there was no relation between the incidence of abnormal laboratory findings and the MID (Table 2).

Table 2 Incidence of abnormal laboratory data and mean initial dose（MID）

	MID <mean initial dose> (mg)			
	≦200	200＜ ≦300	300＜ ≦400	400＜
Crt	2.1%(1)	2.1%(1)	0.0%(0)	0.0%(0)
BUN	2.1%(1)	6.3%(3)	0.0%(0)	0.0%(0)
AST or ALT or ALP	4.2%(2)	10.4%(5)	2.1%(1)	4.2%(2)
Plts	0.0%(0)	2.1%(1)	0.0%(0)	0.0%(0)

Discussion

The glycopeptide antibacterial drugs, vancomycin and teicoplanin, are widely used for the therapy of infections caused by severe or multi drug-resistant gram-positive bacteria. It is known that vancomycin has a narrow therapeutic range, and its pharmacokinetics - volume of distribution and clearance - are considerably affected by the host's condition. Therapeutic drug monitoring (TDM) has, therefore, been employed to determine the optimal dose, thus decreasing the incidence of side effects and enhancing the cost-effectiveness. Teicoplanin, however, has some advantages over vancomycin, in that it has less potential for nephrotoxicity and histamine release 5). Monitoring of the serum level of vancomycin is mandatory in all patients for safety reasons. For teicoplanin, this monitoring is recommended only in patients who are hemodynamically unstable, and in patients with serious infections 6). Wood has reported that the monitoring of teicoplanin serum concentration is needed only to ensure that a therapeutic concentration is achieved 1).

In this context, we performed TDM to design an individual administration regimen for teicoplanin. Patients with poor responses were found to have the lowest mean trough levels, and even in some patients with renal dysfunction, the loading dose of 400 mg followed by maintenance doses of 200 mg did not guarantee the

recommended serum concentration; that is, a trough level of 10-15 μg/ml. We focused on the relationship between the mean dose for the first 3 days (MID) and the trough level before the 4th day, and clinical efficacy. When the MID, calculated as the total dose over the first 3 days / 3, was 266.7 mg or less, the trough level before the 4th day did not exceed 10 μg/ml, which means this dose regimen is inappropriate for initiating therapy for infections.

Several studies have investigated the relationship between serum concentrations of glycopeptides and outcomes 7). The pre-dose serum concentrations are useful in predicting clinical outcome 8). Bantar et al. enrolled 15 patients to assess the efficacy of teicoplanin, 6mg/kg given daily during the first 3 days and then on alternate days, for the treatment of MRSA infections. The mean serum levels of teicoplanin were 22, 8 and 6.7 μg/ml for the peak and the 24-h and 48-h troughs, respectively. The dosage employed in that study proved effective for the treatment of soft tissue and catheter-associated infections 9). Harding et al. showed that the two most readily quantifiable factors that influenced outcome were the mean predose serum concentration and the patient's age - that is, the probability of successful treatment increased with predose serum concentration and decreased with age 8). MacGowan et al. precisely reviewed 12 reports; 6 studies in which a 200 mg/day maintenance dose

of teicoplanin was used, and 6 studies with a 400 mg/day maintenance dose. The mean trough levels in the former 6 studies did not exceed 10 μg/ml in the first 7 days. In the latter 6 studies, the mean trough levels ranged from 4 to 11 μg/ml on days 1-2, 9 to 17 μg/ml on days 6-7 of therapy. In 5 of these studies, the mean trough levels were less than 10 μg/ml on days 1-2. MacGowan et al. concluded that trough levels and post-dose teicoplanin concentrations may be related to clinical outcomes 10). A logistic regression analysis from the same group demonstrated that the probability of successful treatment with teicoplanin declined with age and increased with the mean predose serum concentration.

Glycopeptide antibacterial agents such as teicoplanin are known to show no concentration-dependent killing; this emphasizes the importance of trough levels, because the trough level is closely related to time above the minimum inhibitory concentration (MIC). Transient high peak serum concentrations of teicoplanin are not likely to be of benefit in killing bacteria or curing infection. On the other hand, sustained concentrations over the MIC were said to be of benefit in terms of improving extravascular drug penetration and cure rates 11). Craig recently reported that the 24-h AUC-MIC is probably the most important pharmacokinetic-pharmacodynamic (PK-PD) parameter correlated with the efficacy of vancomycin and teicoplanin 12).

Additional studies are needed to clarify further the pharmacodynamics of teicoplanin. In general, the initial period of therapy is of critical importance in treating infections with teicoplanin. In the present study, patients treated with MID of 266.7mg or less (400mg for loading, 200mg over the 2nd and 3rd days) did not reach the 10 μ g/ml trough level, while most patients treated with an MID greater than 533.3mg (800mg for loading, 400mg over the 2nd and 3rd days) had significant trough levels. Even in the patients with renal dysfunction, the trough levels were appropriate when they were treated with an MID greater than 533.3mg.

For teicoplanin, there are data linking the predose concentrations to the toxicity of thrombocytopenia 7). Thus, increases in the trough and/or MID values may cause higher incidences of abnormal data. However, in the present study, no relation was found between abnormal data and MID levels of 533.3mg or less. Bibler et al. showed that the most significant adverse reaction to teicoplanin was an urticarial rash, which required discontinuation of therapy in one patient. Pruritus, rash, eosinophilia, and transaminase elevation have been reported occasionally 13).

We conclude that, for teicoplanin, 800mg as an initial dose, followed by 400mg for 2 days can be recommended to promptly and safely obtain an optimal trough level.

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Legends for Figures

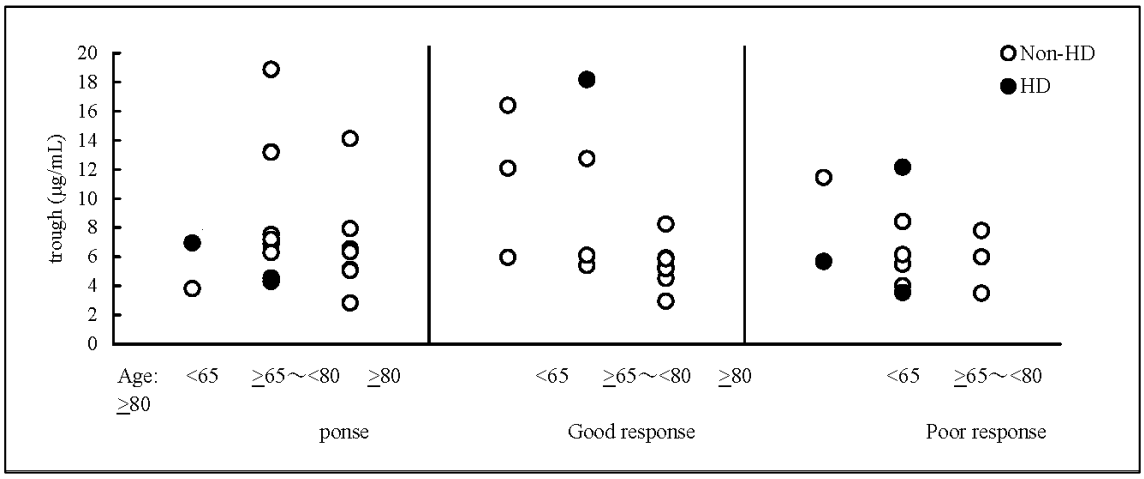

Fig1: The relationship between the clinical efficacy, patients' ages, and serum trough levels of teicoplanin before the 4th day of administration. *HD*, hemodialysis

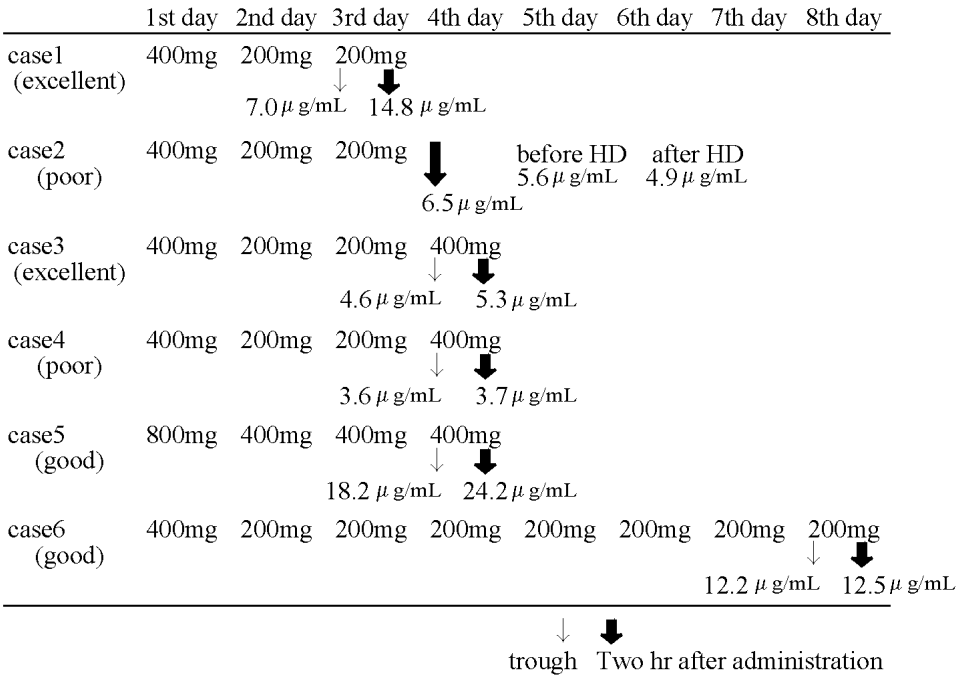

Fig2: Administered doses of teicoplanin and their trough levels (*narrow arrow*) and the serum concentrations 2h after administration (*thick arrow*) in six patients with renal dysfunction.

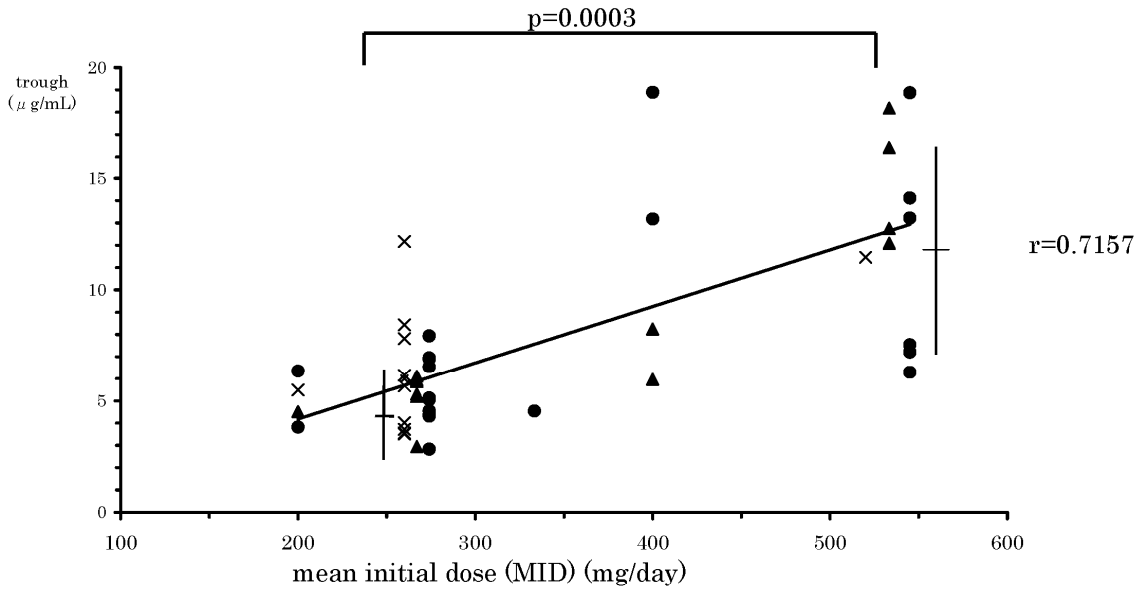

Fig3: Trough levels of teicoplanin at the point before the 4th day of administration (Cpre) in 48 patients, mean initial dose (*MID*), and efficacy. *Crosses* show poor response; *triangles*, good response; and *dots*, excellent response. See text for definition of efficacy. Cpre values were closely correlated with higher MID.

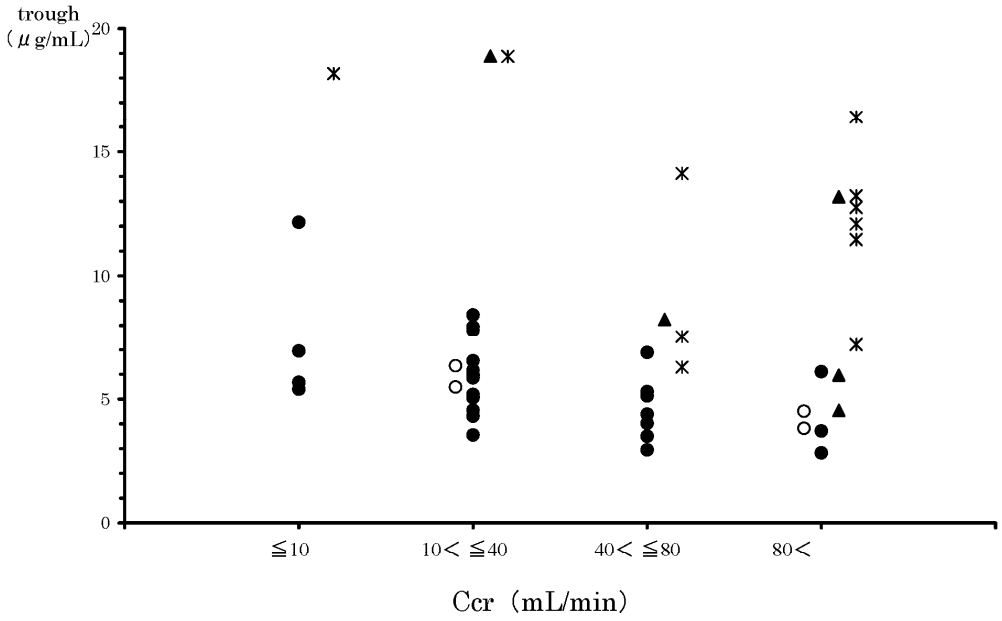

Fig4: The relation between trough levels of teicoplanin before the 4th day of administration (Cpre), creatinine clearance (*Ccr*) in 40 patients and the MID. *Circles*, MID ≦200mg; *dots*, ＞200 to ≦300mg; *triangles*, ＞300 to ≦400mg; *asterisks*, ＞400 to ≦800mg.