Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose

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Data obtained as part of our routine drug monitoring of teicoplanin therapy (therapeutic drug monitoring, TDM) in adult critically ill patients being treated for suspected or documented Gram-positive multiresistant infections were assessed, retrospectively. Data were available for 202 patients (146 male, 56 female; age 58 ± 16 years) with a total number of 829 teicoplanin trough plasma levels (Cmin) assessed. The percentage of patients with adequate teicoplanin concentrations (Cmin ≥ 10 mg/L) during the treatment period substantially increased from 3.2% on day 2, to 35%, 70%, 90% and ∼95% on days 4, 7, 11 and 15, respectively. The findings suggest that optimal teicoplanin therapy was achieved only after at least 4, and probably 7, days of therapy in most cases, mainly because of a failure to use an appropriate loading dose. Among the possible causes for the reluctance to use a loading dose, concern over the potential nephrotoxicity of teicoplanin was a major factor. We conclude that loading doses of teicoplanin (6 mg/kg every 12 h for at least three doses) must be considered mandatory in all patients, regardless of their renal function, to enable optimal drug concentrations to be achieved early in the treatment period. Subsequently, TDM is important to ensure that dose regimens are optimized to the individual requirements of the patients.

Keywords: teicoplanin, TDM, loading dose, renal function, hypoalbuminaemia

Introduction

Severely ill patients in intensive care units (ICU), haematological or cardiosurgical wards, and in those undergoing haemodialysis, are frequently at risk of developing Gram-positive multiresistant bacterial infections. Data from the National Nosocomial Infections Surveillance (NNIS) System indicated that coagulase-negative staphylococci, Staphylococcus aureus and enterococci, species with a high incidence of multiresistant strains, were the most frequently reported hospital-acquired bloodstream infection isolates between 1992 and 1999, accounting for 63% of all such isolates.

Glycopeptide antibiotics have long been considered the gold standard for treatment of documented or suspected life-threatening multiresistant Gram-positive bacterial infections, and whereas vancomycin is the sole glycopeptide available in the USA, teicoplanin represents a widely available alternative in Europe.

Although the need for therapeutic drug monitoring (TDM) of vancomycin has been recognized for many years, in recent years the TDM of teicoplanin has been increasingly highlighted as important. It is generally accepted that whereas a trough plasma level of >10 mg/L is appropriate for the majority of severe infections, 20 mg/L should be exceeded for endocarditis and bone or prosthetic infections.

In this study, we have analysed, retrospectively, results from the TDM of teicoplanin carried out at our institute during the last 7 years in order to determine how frequently the recommended concentrations are achieved in critically ill patients.

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Materials and methods

This study retrospectively assessed data obtained between October 1995 and March 2002 as part of our routine TDM of teicoplanin therapy in adult critically ill patients who were being treated for suspected or documented Gram-positive multiresistant infections.

At our institution, guidelines for appropriate teicoplanin use are an initial loading dose of 6 mg/kg every 12 h for three doses (regardless of renal function), followed by a maintenance dose based on both the patient’s renal function and TDM results. Although teicoplanin TDM is not carried out on all patients, it is usually carried out in those that are severely ill or those presenting with pathophysiological conditions that may affect teicoplanin disposition.

The objective of the study was to determine the percentage of patients that achieve adequate concentrations of teicoplanin.

Adequate drug exposure was defined as a trough plasma concentration \( C_{\text{min}} \) of 10 mg/L or greater, and is that which is largely accepted in routine clinical practice as the minimum threshold for optimal drug exposure for the majority of serious infections.

To assess renal function, serum creatinine concentrations were determined at the same time as each TDM was carried out, and creatinine clearance (CLCR) was then estimated on the basis of the Cockcroft & Gault formula. Patients were considered to have normal renal function when CLCR was >50 mL/min, moderately impaired renal function when CLCR was between 20 and 50 mL/min and total renal failure when it was below 20 mL/min.

TDM of teicoplanin was initially carried out after the patient had received teicoplanin for at least 24 h and then repeated according to the length of therapy and to the patient’s pathophysiological status. Blood samples for TDM were collected immediately before the morning teicoplanin administration. After centrifugation at 3000 rpm for 10 min, plasma samples were analysed within 2 h by means of a fluorescence polarization immunoassay (Opus Diagnostics, Fort Lee, NJ, USA) using a TDX analyser (TDx, Abbott, Rome, Italy). The inter-day and intra-day coefficients of variation of the assay were <10%. Teicoplanin dosing regimens were then individualized on the basis of TDM results to achieve and maintain \( C_{\text{min}} \geq 10 \text{ mg/L} \).

Statistical analysis

Descriptive data were expressed as mean ± S.D. or median and range, according to whether the data distribution was normal or non-normal, respectively. Statistical analyses comparing TDM data between different groups were carried out using a parametric (paired or unpaired Student’s t-test, as appropriate) or non-parametric (Mann–Whitney rank sum test) test for normal or non-normal distributed data, respectively, by means of SigmaStat software (SPSS Science Software, GmbH, Erkrath, Germany). A multivariate analysis was carried out in order to evaluate which factors among dose/kg of teicoplanin, CLCR, age and albuminaemia might have influenced teicoplanin \( C_{\text{min}} \). A value of \( P < 0.05 \) was required to achieve statistical significance.

Results

The characteristics of the 202 critically ill patients included in the study are shown in Table 1. Patients were hypoalbuminaemic in 74.5% of cases and presented with normal, moderately or totally impaired renal function in 52.4%, 20.1% and 27.5% of cases, respectively. Four of the 202 patients (2.0%) had a significant reduction of renal function (increase in serum creatinine >0.5 mg/dL) either during or following teicoplanin treatment. Three of these four patients were co-treated with another nephrotoxic drug (amikacin, netilmicin or cyclosporin), and it was not possible to identify whether the change in renal function had been caused by teicoplanin. The renal impairment observed after >3 weeks of teicoplanin therapy in the fourth patient might have theoretically been teicoplanin related.

The mean ± S.D. administered total daily dosage of teicoplanin was 7.23 ± 3.08, 4.53 ± 3.09 and 3.61 ± 1.93 mg/kg in patients with normal, moderately or totally impaired renal function, respectively. The total number of teicoplanin TDM samples assayed was 829, with the median of three TDM samples for each patient.

The teicoplanin concentrations for 202 patients are shown in Figure 1. Mean teicoplanin \( C_{\text{min}} \) was 4.98, 7.64 and 9.40 mg/L on days 2, 3 and 4, respectively, increasing to values of ≥10 mg/L from day 5 on. Unfortunately, because

Table 1. Patients’ characteristics and treatments

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>202</td>
</tr>
<tr>
<td>Gender</td>
<td>146M, 56F</td>
</tr>
<tr>
<td>Age (years)(a)</td>
<td>58 ± 16</td>
</tr>
<tr>
<td>Body weight (kg)(a)</td>
<td>73 ± 16</td>
</tr>
<tr>
<td>Albuminaemia (g/L)(a)</td>
<td>3.09 ± 0.88</td>
</tr>
<tr>
<td>Patients with normal renal function</td>
<td>106</td>
</tr>
<tr>
<td>Patients with moderately impaired renal function</td>
<td>41</td>
</tr>
<tr>
<td>Patients with totally impaired renal function</td>
<td>55</td>
</tr>
<tr>
<td>Days with teicoplanin therapy(b)</td>
<td>9 (3–53)</td>
</tr>
<tr>
<td>Total TDM samples</td>
<td>829</td>
</tr>
<tr>
<td>Number of TDM for each patient(b)</td>
<td>3 (2–26)</td>
</tr>
</tbody>
</table>

\(a\) Calculated with the Cockcroft & Gault formula; \(b\) TDM, therapeutic drug monitoring.

\(\text{CLCR} \) estimated creatinine clearance by means of the Cockcroft and Gault formula; TDM, therapeutic drug monitoring.

\(\text{Data are expressed as mean ± S.D.}\)

\(\text{Data are expressed as median and range.}\)
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this was a retrospective analysis, not all patients were sampled on each of the days of therapy.

The percentage of patients with teicoplanin $C_{\text{min}} \geq 10 \text{ mg/L}$ during the treatment period increased from 3.2% on day 2 to 35%, 70%, 90% and 95% on day 4, 7, 11 and 15, respectively.

When we evaluated whether patients had received a loading dose during the first 4 days of therapy, we observed that an appropriate loading dose of teicoplanin (6 mg/kg every 12 h for at least three doses) was administered only in 38.6% of cases. Loading doses were administered to 41.2% of patients presenting with normal renal function and to 8.7% and 2.2% of patients presenting with moderately or totally impaired renal function, respectively. Patients who received a loading dose (average of 5.84 mg/kg every 12 h for at least three doses) had significantly higher $C_{\text{min}}$ concentrations than those who received only a maintenance dose (average of 4.67 mg/kg per daily) estimated from the degree of renal function. The mean trough concentrations of teicoplanin in those patients that received a loading dose compared with those that did not (Figure 2) were: 6.47 versus 4.24 mg/L on day 2 ($P=0.001$), 10.80 versus 6.11 mg/L on day 3 ($P<0.001$) and 11.22 versus 8.66 mg/L on day 4 ($P=0.022$).

Multivariate analysis indicated that the only factor significantly correlated with teicoplanin $C_{\text{min}}$ (both with actual and normalized dose per kg teicoplanin values) on days 2 and 3 of therapy was the administered dose/kg, whereas other factors besides dose/kg, namely CLCR and age, appeared to be inversely correlated with teicoplanin trough levels on day 4 (Table 2).

**Discussion**

The results of this study would suggest that optimal therapy with teicoplanin was achieved only after at least 4 days of therapy in most of the patients studied. These inadequate

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**Figure 1.** Mean (± S.D.) trough plasma levels of teicoplanin in critically ill patients. The dotted line is the minimum concentration recommended in serious infection (10 mg/L).

**Figure 2.** Mean (± S.D.) trough plasma levels of teicoplanin during the first days of therapy in patients receiving (filled symbols) versus those not receiving (open symbols) a loading dose. The dotted line is the minimum concentration recommended in serious infection (10 mg/L).

**Table 2.** Results of multiple linear regression analysis to assess the factors influencing teicoplanin trough plasma levels ($C_{\text{min}}$) during the first days of therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>coeff. S.E. t P value</td>
<td>coeff. S.E. t P value</td>
<td>coeff. S.E. t P value</td>
</tr>
<tr>
<td>Dose/kg</td>
<td>0.288 0.086 3.330 0.002</td>
<td>0.620 0.129 4.820 &lt;0.001</td>
<td>0.758 0.139 5.447 &lt;0.001</td>
</tr>
<tr>
<td>CLCR/kg</td>
<td>-0.276 0.548 -0.503 0.617</td>
<td>-0.599 0.811 -0.739 0.462</td>
<td>-2.885 0.730 -3.952 &lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.049 0.025 -1.979 0.053</td>
<td>-0.012 0.038 -0.328 0.744</td>
<td>-0.133 0.029 -4.672 &lt;0.001</td>
</tr>
<tr>
<td>Albuminaemia</td>
<td>0.080 0.292 0.275 0.785</td>
<td>0.082 0.519 0.158 0.875</td>
<td>-0.346 0.408 -0.848 0.399</td>
</tr>
</tbody>
</table>

CLCR, estimated creatinine clearance by means of the Cockcroft and Gault formula; coeff., coefficient of the independent variables; S.E., standard error of the regression coefficients; t, ratio coeff./S.E.; P value, P value calculated for t.
concentrations in the first days of therapy may possibly affect outcome of teicoplanin therapy, although this was not specifically addressed in our study. It should not be overlooked that when Gram-positive bacteria presenting with an MIC of teicoplanin close to the breakpoint may be the concern, clinical failure and microbiological resistance to glycopeptides may occur because of subtherapeutic concentrations. Harding et al. using a logistic regression model, demonstrated that the probability of success with teicoplanin for the treatment of S. aureus septicaemia increased with trough serum concentration and decreased with age, concluding that trough levels of teicoplanin should always exceed 10 mg/L, especially in the elderly, to enable cure of S. aureus-related septicaemia.

A possible explanation for the low teicoplanin levels found in the first 4 days of therapy may be the low percentage of patients who received appropriate loading doses of teicoplanin (6 mg/kg every 12 h for at least three doses). Although teicoplanin has been in clinical use for >10 years, with concerns about its schedule regimen highlighted in the early 1990s, inappropriate use still continues to exist in clinical practice, due in part to the unusual pharmacokinetic characteristics of this antibiotic. Despite its hydrophilic nature and a low volume of distribution (<1 L/kg), teicoplanin has a long elimination half-life (30–170 h) as a result of its high plasma protein binding (>90%), which greatly reduces renal clearance. Although these pharmacokinetic parameters allow once-daily dosing, the prolonged half-life means that steady-state conditions are only achieved after several days, and an initial loading dose (6 mg/kg every 12 h for at least three doses) has to be administered to achieve therapeutically relevant plasma concentrations early in the treatment period.

Of the patients with impaired renal function, most (>90%) did not receive the loading dose. Although several reports have documented that teicoplanin is less nephrotoxic than vancomycin and clinicians within our institute are advised of the importance of teicoplanin loading doses, it is clear that many clinicians do not follow this advice. Unfortunately, there is no rationale for this approach since if a loading dose is needed because of the drug pharmacokinetic characteristics, it must be given to all of the patients, irrespective of their renal function, as the requirement for loading depends exclusively on the volume of distribution and target concentration and not on the drug clearance.

The multivariate analysis indicated that teicoplanin C_{min} concentrations during the first few days of therapy were directly influenced only by the dose/kg, but from day 4 on they were also influenced by the renal clearance, as shown by the significant inverse relationship with CL\textsubscript{CR} and age. Therefore, after an initial period of loading dose administration in the first 2 days, maintenance doses have then to be adjusted according to patients’ CL\textsubscript{CR} and TDM results in the following days to avoid under- or over-dosing.

Although albuminaemia was not found to be a significant covariate of teicoplanin C_{min} in this study, this may have been compounded by the fact that most of our patients (75%) were hypoalbuminaemic. Certainly, the hypoalbuminaemia found in most of our patients may partially account for the low teicoplanin levels seen, since teicoplanin is a highly albumin-bound drug and it is known that under such conditions more rapid distribution and higher clearance may both occur.

A reassuring finding of this study is that the percentage of patients with therapeutically adequate teicoplanin levels substantially increased in response to TDM. These findings emphasize the important role of TDM in tailoring teicoplanin dose regimens, particularly in critically ill patients, as this population frequently presents with peculiar pathophysiological conditions that potentially affect the disposition of many antibiotics.

In conclusion, appropriate loading doses of teicoplanin (6 mg/kg every 12 h for three doses) must be considered mandatory for all patients, regardless of their renal function, in order to achieve therapeutically relevant concentrations early in the treatment period. Subsequently, TDM is important to ensure that dose regimens are optimized to the individual requirements of the patients.

References

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