Analyses of teicoplanin concentrations from 1994 to 2006 from a UK assay service

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Received 14 December 2009; returned 28 January 2010; revised 15 June 2010; accepted 18 June 2010

Objectives: An analysis of the trough serum concentrations sent to the UK Antimicrobial Reference Laboratory for teicoplanin therapeutic drug monitoring (TDM).

Methods: All trough concentrations over a 13 year period were analysed and the percentages were calculated for the following:

1. <10 mg/L (a sub-optimal concentration for all);
2. ≥10–<20 mg/L (the target used for ordinary Gram-positive infections);
3. ≥20–<60 mg/L (the target for all severe staphylococcal infections including endocarditis); and
4. ≥60 mg/L (the concentration associated with toxicity).

Results: The percentage of patients with concentrations of <10 mg/L decreased each year to 13% in 2006. Almost 40% of the samples each year were in the ≥10–<20 mg/L range. In 1996, the percentage of samples in the ≥20–<60 mg/L range reached a study high of ≈70%. That percentage then fell to 30% and increased slowly to 50% at the end of the study. Fewer than 5% of the samples were ≥60 mg/L.

Conclusions: Our study shows that there is a need to increase the initial dose or extend the number of days that the loading dose is used in a significant number of patients. With such a wide optimal range and a low potential for toxicity, it is unclear why optimal therapy is not achieved in a higher percentage of patients.

Keywords: glycopeptides, pharmacokinetics, patients

Introduction

Teicoplanin is a glycopeptide antibiotic that was introduced to the UK market in 1990. It has become, along with vancomycin, one of the treatments of choice for severe Gram-positive sepsis, including infections caused by methicillin-resistant Staphylococcus aureus (MRSA). Teicoplanin has a wide variation in serum half-life, which varies from 69 to 327 h. As the half-life is prolonged, once daily dosing is recommended, though it takes a considerable time to reach steady state. One study has suggested that with a clinical half-life of 60 h and once daily dosing it would take 10 days to reach steady state. Therefore, the use of a 12 hourly loading dose for the first 3 days of treatment followed by a daily dose of at least 6 mg/kg is recommended to ensure that patients reach therapeutic concentrations early in their course of treatment.

Sub-optimal teicoplanin concentrations have been associated with treatment failure. They are also regarded as a possible risk factor for microbiological resistance to glycopeptides. Pea et al. found optimal teicoplanin concentrations were achieved only after 4 days of treatment in the majority of their patients. They highlighted the possibility that the loading dose used may have been inadequate. Harding et al. showed that the probability of treatment success with teicoplanin for S. aureus septicaemia increased with the serum concentration. They concluded that trough concentrations of teicoplanin should be >10 mg/L for successful treatment. This is reflected in the British National Formulary, which recommends that, for S. aureus infections, a trough concentration of >10 mg/L should be achieved. However, this concentration needs to be >20 mg/L for more severe staphylococcal infections, such as endocarditis and osteomyelitis.

Therapeutic drug monitoring (TDM) of teicoplanin is recommended to help with patient maintenance. However, as evidence in the literature suggests, TDM is still not widely practised.

The Antimicrobial Reference Laboratory has been providing an assay service for the UK and for teicoplanin since 1994. The aim of this study was to analyse the teicoplanin pre-dose serum concentrations in patient samples referred for TDM and determine whether optimal concentrations were achieved.

Materials and methods

Assay

Serum samples sent to our laboratory for TDM were measured in 1994 by a validated HPLC method and, subsequently, by a polarization
Table 1. Summary of the patient data used in the analysis and the median concentrations each year

<table>
<thead>
<tr>
<th>Year</th>
<th>Samples, n</th>
<th>Hospitals, n</th>
<th>Patients, n</th>
<th>Age range</th>
<th>Median concentration, mg/L (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>226</td>
<td>44</td>
<td>132</td>
<td>&lt;1 month to 91 years</td>
<td>16.7 (&lt;5–50.7)</td>
</tr>
<tr>
<td>1995</td>
<td>379</td>
<td>70</td>
<td>209</td>
<td>3 months to 92 years</td>
<td>14.7 (&lt;5–181.2)</td>
</tr>
<tr>
<td>1996</td>
<td>392</td>
<td>68</td>
<td>246</td>
<td>2 months to 92 years</td>
<td>14.5 (&lt;5–74.6)</td>
</tr>
<tr>
<td>1997</td>
<td>610</td>
<td>81</td>
<td>375</td>
<td>&lt;1 month to 96 years</td>
<td>15.0 (&lt;5–110.9)</td>
</tr>
<tr>
<td>1998</td>
<td>904</td>
<td>100</td>
<td>554</td>
<td>&lt;1 month to 95 years</td>
<td>16.6 (&lt;5–210.3)</td>
</tr>
<tr>
<td>1999</td>
<td>827</td>
<td>109</td>
<td>540</td>
<td>2 months to 99 years</td>
<td>16.9 (&lt;5–170.6)</td>
</tr>
<tr>
<td>2000</td>
<td>968</td>
<td>109</td>
<td>588</td>
<td>&lt;1 month to 96 years</td>
<td>17.5 (&lt;5–168.2)</td>
</tr>
<tr>
<td>2001</td>
<td>1034</td>
<td>126</td>
<td>652</td>
<td>1 month to 97 years</td>
<td>17.3 (&lt;5–202.5)</td>
</tr>
<tr>
<td>2002</td>
<td>822</td>
<td>122</td>
<td>546</td>
<td>&lt;1 month to 98 years</td>
<td>18.0 (&lt;5–130.3)</td>
</tr>
<tr>
<td>2003</td>
<td>993</td>
<td>134</td>
<td>667</td>
<td>&lt;1 month to 96 years</td>
<td>19.4 (&lt;5–186.0)</td>
</tr>
<tr>
<td>2004</td>
<td>1001</td>
<td>125</td>
<td>657</td>
<td>1 month to 96 years</td>
<td>18.1 (&lt;5–168.8)</td>
</tr>
<tr>
<td>2005</td>
<td>1134</td>
<td>141</td>
<td>691</td>
<td>&lt;1 month to 100 years</td>
<td>18.6 (&lt;5–135.6)</td>
</tr>
<tr>
<td>2006</td>
<td>1007</td>
<td>121</td>
<td>737</td>
<td>1 month to 100 years</td>
<td>21.8 (&lt;5–263.5)</td>
</tr>
</tbody>
</table>

Figure 1. Percentage of samples that were <10, ≥10–<20, ≥20–<60 and ≥60 mg/L.

Data analysis

A retrospective analysis was carried out on all trough samples received between January 1994 and December 2006, using Microsoft Access and Excel. Unfortunately, due to implementation of a new data analysis and document management system in 2007, data collected after this point were incompatible with those collected earlier and could not be analysed together with the data presented in this manuscript. An analysis was carried out to assess the percentage of the trough teicoplanin concentrations that were sub-optimal for general staphylococcal infections (<10 mg/L) and for more severe infections (<20 mg/L). A further analysis was made to calculate the percentage of the concentrations that had the potential to cause toxicity (≥60 mg/L). We included all age groups of patients in our analysis. Two very high concentrations, 476 and 900 mg/L, which may have resulted from being taken through an intravenous line, were excluded from the analysis.

Results

During the study period, the total number of assay requests and the number of requesting hospitals increased each year, reaching a peak in 2005 when we received 1134 samples (Table 1). Over the 13 year period, 1994–2006, the median trough teicoplanin concentration increased from 16.7 mg/L to 21.8 mg/L, i.e. to one optimal for all types of infections (Table 1). The percentage of patients with sub-optimal (<10 mg/L) teicoplanin concentrations for general staphylococcal infections was found to have decreased over the study period from 23% in 1994 to 13% in 2006 (Figure 1). With the exception of the early years, when there were fewer requests, there was a general increase in the percentage of samples with concentrations in the optimal range for serious MRSA infection (≥20–<60 mg/L) over the study period, ranging from 33% in 1997 to 49% in 2006 (Figure 1).

Teicoplanin trough concentrations of ≥60 mg/L, with the potential to cause toxicity, remained few throughout the study period (Figure 1). The highest number was in 2006, when 3.4% of the samples had concentrations of ≥60 mg/L.

Discussion

In this study, a large number of teicoplanin samples, in excess of 10,000, were analysed. These came from a wide selection of UK hospitals (Table 1). The increased use of teicoplanin in the 1990s was reflected by a rapid rise in the number of samples that were referred to us for assay. Changes in the teicoplanin dosing in the data sheet meant that by 2006 the median trough concentration was ≥20 mg/L. However, despite this increase in the concentration, one-third of the patients still had sub-optimal concentrations of <20 mg/L for MRSA infections. For other types of Gram-positive infection, the trough teicoplanin concentrations considered sub-optimal (<10 mg/L) decreased over the study period from 23% to 13%.

Throughout the study period, the number of trough concentrations with the potential to cause toxicity (≥60 mg/L) were few. The principal purpose of TDM for teicoplanin is to ensure optimal concentrations are achieved and then maintained. Teicoplanin has a very wide optimal range, from 20 to 60 mg/L.

Although underdosing with teicoplanin has been highlighted as a significant concern on a number of occasions, the reasons for underdosing remain poorly studied and it has been generally assumed that underdosing results from a failure to follow data sheet recommendations on loading doses.
However, a recent study modelling the pharmacokinetics of thrice weekly teicoplanin in an outpatient setting has highlighted that, to achieve optimal concentrations, doses considerably higher than those recommended in the data sheet need to be used. Combined with the finding of this study that a significant proportion of patients fail to achieve optimal concentrations, this would suggest that a re-evaluation of current teicoplanin dosing guidelines is warranted so as to ensure that more patients reach therapeutic concentrations and that these are achieved early in their dose regimen.

**Funding**
This research was carried out as part of routine assay work.

**Transparency declarations**
None to declare.

**References**