Teicoplanin levels in bone and joint infections: Are standard doses subtherapeutic?☆

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Summary  Objectives: Previously published data suggest that a trough serum teicoplanin level of ≥20 mg/l is predictive of improved outcomes in serious staphylococcal infection. We investigated how dose regimen and patient characteristics impact on trough teicoplanin levels in patients with musculoskeletal infection, in order to help standardise teicoplanin use.

Methods: We prospectively collected data for 141 clinically stable adults with bone and joint infection treated as outpatients with teicoplanin. Patients with end stage renal failure were excluded.

Results: The most frequently used teicoplanin dose regimens were 400 mg or 600 mg iv once daily. Trough levels were available for 78% of episodes, of which 51% were ≥20 mg/l. Unsurprisingly, a level of ≥20 mg/l occurred more often with a dose of 600 mg than with lower doses (p = 0.005). There was no significant relationship between teicoplanin level and age, body weight or creatinine clearance, but male gender was associated with lower trough levels than female gender (p = 0.03).

Conclusions: These data suggest that teicoplanin levels of ≥20 mg/l for bone and joint infection in stable adult patients are best achieved with a daily dose of at least 600 mg.

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Introduction

Teicoplanin is a glycopeptide antibiotic discovered in 1978, introduced into the UK market in 1991, and now widely used for the treatment of serious gram positive infection. Administration may be by the intravenous (iv) or intramuscular (im) route, and the long elimination half-life permits once daily dosing. In animal models, teicoplanin has been shown to penetrate into musculoskeletal tissues, and it has become a common choice in the parenteral treatment of bone and joint infection. The cost of teicoplanin acquisition in the UK has fallen over time, and use of teicoplanin for outpatient therapy is a cost effective strategy.

Teicoplanin dose regimes should aim to maintain drug concentrations above the MIC of the pathogen at the site of infection. However, there is a lack of consistency in teicoplanin prescribing based on clinicians’ differing familiarity with the agent, cost of acquisition, efficacy concerns, and the accessibility and interpretation of drug assays.

In the treatment of musculoskeletal infections, larger doses and higher levels of teicoplanin have generally correlated with improved clinical outcomes. In particular, higher drug doses and levels have been advocated for the successful treatment of septic arthritis. Higher mean trough levels (≥20 mg/l) have also been correlated with improved outcome in the treatment of endocarditis, blood stream infection, and pneumonia.

Advocated teicoplanin dose regimens vary from 200 mg to 800 mg (or from 3 mg/kg to 12 mg/kg body weight) once daily, with a single additional loading dose. The UK teicoplanin data sheet (Aventis) recommends treatment of osteomyelitis with 400 mg once daily (or 6 mg/kg in patients weighing more than 85 kg), and treatment of septic arthritis with 800 mg (or 12 mg/kg). The British National Formulary advocates a standard daily dose of 400 mg, but advises that higher doses may be required in patients over 85 kg and in treatment of methicillin-resistant Staphylococcus aureus (MRSA) infection (http://www.bnf.org/bnf/). Some sources suggest that higher doses (≥10 mg/kg) may be required to achieve adequate bactericidal concentration in bone, highlighting the challenge of achieving adequate antibiotic penetration for the successful treatment of deep cortical infection or bone infection associated with prosthetic material. Other dosing schedules include the use of additional loading doses to reduce the time taken to reach therapeutic levels, and alternate daily dosing.

Monitoring trough (pre-dose) teicoplanin levels is recommended for patients with severe infection in order to ensure that therapeutic levels are achieved. As serious side-effects with teicoplanin are uncommon, monitoring peak serum concentrations is not routine practice. However, many hospitals do not routinely undertake therapeutic drug monitoring for patients receiving teicoplanin.

Given the lack of consistency in choice of dose regimens, the range of prescribing recommendations, and the variable use of drug assays, we have investigated the teicoplanin levels attained in a stable adult population with musculoskeletal infections in order to help guide future practice.

Patients and methods

In our bone infection unit (BIU), teicoplanin is commonly used for outpatient treatment of bone and joint infection. In this patient group, total treatment duration with glycopeptide is commonly 4–6 weeks; this is frequently vancomycin for in-patients, which is switched to teicoplanin on discharge (for reasons of cost and ease of drug administration in the community).

We studied consecutive adult patients (age ≥16 years) with bone and joint infection treated with outpatient parenteral teicoplanin under the care of BIU physicians and the Oxfordshire Primary Care Trust Home IV team over a period of 17 months, commencing April 2005. We excluded patients needing in-patient care for the duration of their therapy, and those with end-stage renal failure (defined as needing renal replacement therapy).

We prospectively recorded demographic data, clinical diagnoses, teicoplanin dose regimens and drug levels on a Microsoft Access database. Bacteriology results were ascertained retrospectively from the laboratory computer system. A microbiology diagnosis was confirmed by two or more samples from the same site yielding indistinguishable organisms.

We aimed to take blood for teicoplanin trough levels at 6–8 days into therapy, allowing this time interval to ensure that steady state had been reached, with target trough levels between 20 and 60 mg/l. If levels are outside this range, dose was modified and levels were repeated after a further interval of 6 days when possible. The regional Antimicrobial Reference Laboratory (North Bristol NHS Trust) performs our trough serum teicoplanin levels using a fluorescence polarisation immunoassay, and recommends trough levels between 10 and 60 mg/l (or between 20 and 60 mg/l for Staphylococcus aureus infection).

The teicoplanin minimum inhibitory concentration (MIC) for isolates of MRSA and coagulase negative staphylococci from sterile site samples was undertaken by our laboratory using Epsilometer tests (E-tests) (Bio-stat Ltd). MIC testing was not routinely done for methicillin-susceptible S. aureus.

Results

Patient demographics and diagnosis

We studied 141 patient episodes (98 male, 43 female), with a median age of 63 years (range 16–89), all of whom were treated in the community with teicoplanin. Cases originated predominantly from the BIU (accounting for 68%) and orthopaedic wards (17%); other patients were referred from infectious diseases, cardiology and diabetology units. Primary diagnosis was osteomyelitis in 74 patients, prosthetic joint infection in 55 and native joint septic arthritis in 12 (Fig. 1a). Comorbidities included diabetes mellitus in 21 patients (15% of the total cohort) and other conditions associated with immunocompromise in 12 patients (Table 1).

Coagulase negative staphylococci and S. aureus were the commonest laboratory isolates treated with
teicoplanin, identified in pure culture in 44 (31%) and 27 (19%) patients respectively (Fig. 1b). Of the S. aureus isolates, 22 (81%) were MRSA. Polymicrobial infection (defined as ≥2 different organisms in ≥2 tissue samples on the same date) accounted for 24 (17%) episodes, 14 of which included a gram negative component. Cultures were sterile in 26 (18%) of episodes. Teicoplanin MICs for coagulase negative staphylococci varied between 0.38 and 4 mg/l, with one outlier of 12 mg/l.

**Teicoplanin dose regimens**

Dose regimens varied from 200 mg once daily (2 patients), to 400 mg once daily (97 patients), or 600 mg once daily (42 patients). The unusually low dose of 200 mg was given at the discretion of the prescribing physician in two patients over the age of 70, both of whom had renal impairment (creatinine clearance <40 ml/min). The selected dose was not statistically associated with patient gender (p = 0.82, Fisher’s exact test), or with age, renal function or total body weight (p = 0.92, p = 0.57, p = 0.51 respectively, Mann–Whitney test). Second episodes of treatment were given to 7 patients during the study time-frame, which may reflect failure of first treatment regime, or serial treatment episodes combined with surgery for multifocal osteomyelitis. Additional antibiotics were only used in the context of co-existent gram negative infection.

**Table 1** Co-morbid medical conditions in 141 adult patients receiving treatment with parenteral teicoplanin for bone and joint infection

<table>
<thead>
<tr>
<th>Condition</th>
<th>Number of patients</th>
<th>Frequency in this cohort (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>27</td>
<td>19.1</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>13</td>
<td>9.2</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25</td>
<td>17.7</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6</td>
<td>4.3</td>
</tr>
<tr>
<td>Cancer</td>
<td>4</td>
<td>2.8</td>
</tr>
<tr>
<td>Thromboembolic disease</td>
<td>2</td>
<td>1.4</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>HIV</td>
<td>1</td>
<td>0.7</td>
</tr>
<tr>
<td>SLE</td>
<td>1</td>
<td>0.7</td>
</tr>
</tbody>
</table>

**Trough serum teicoplanin levels**

A trough teicoplanin level was available for 110 episodes (78% of the total cohort) (Fig. 2). The assay was taken during our recommended window of 6–8 days into therapy in 58 cases (53% of levels), increasing to 84 (76%) taken between day 6 and 12. There was no statistical difference in drug dose, gender, age, or renal function between patients who had trough levels taken and those who did not have therapeutic drug monitoring (p = 0.27, p = 0.51, (Fisher’s exact test); p = 0.16, p = 0.58 (Mann–Whitney test) respectively).

Of 110 trough levels, 56 (51%) were at or above the threshold of 20 mg/l which has been associated with improved outcome in serious infection. Patients receiving 600 mg daily were more likely to achieve levels of ≥20 mg/l than those receiving lower doses; of 30 patients receiving a daily dose of 600 mg, 22 (73%) achieved a level of ≥20 mg/l, while in 78 patients receiving a daily dose of 400 mg or less, 32 (41%) had levels of ≥20 mg/l (p = 0.005, Fisher’s exact test).

The trough level exceeded 60 mg/l (a standard reference range upper limit) in 5 cases (4 male and 1 female,
age range 38–78, creatinine clearance range 65–140 ml/min, daily dose 400 mg in four cases and 600 mg in one). Given the normal renal function and relatively conservative daily doses, these high levels may reflect an artefact of serum sampling from a vascular access device through which teicoplanin had been delivered. For this reason, we have excluded one patient with a level of >100 mg/l from further analysis.

Repeat levels were taken in 7 patients, of whom 2 had initial levels >60 mg/l, 4 had initial levels <20 mg/l, and 1 had a missing first level, despite documentation of serum having been taken. Second levels were between 14.6 and 28.6 mg/l.

Male gender was associated with lower trough teicoplanin levels than female (p = 0.03, Mann–Whitney test). There was no significant relationship between age and trough teicoplanin level (p = 0.65, Spearman correlation). Total body weight, recorded for 96 patients (mean 77 kg, range 45–127 kg), also did not correlate with serum teicoplanin levels (p = 0.43, Spearman correlation). Serum creatinine was available for all patients at the outset of treatment (range 0.1–2.4 mg/dl). Creatinine clearance was calculated using the Cockcroft–Gault formula, ((140 – age) × weight (kg) × (0.85 if female))/((72 × serum creatinine (mg/dl))), for all patients with a recorded weight (range 13–178 ml/min), and did not correlate with trough serum teicoplanin levels (p = 0.50, Spearman correlation).

Side effects and toxicity

Teicoplanin toxicity was reported in seven patients (5% of the cohort), of whom four were receiving a 400 mg daily dose, and three a 600 mg dose (p = 0.43, Fisher’s exact test). Documented side-effects were rash (three patients), shivers or sweats (two patients), and neutropenia (neutrophils <1.5 × 10^9/l) (two patients). Six of these patients had teicoplanin discontinued as a consequence, shortening their intended teicoplanin treatment course by a mean of 8 days. None of the five patients with levels >60 mg/l had documented side-effects but one had a rise in serum creatinine (from baseline 0.85 mg/dl to a maximum of 1.06 mg/dl).

Discussion

At present, teicoplanin dose regimens and use of assays vary between clinicians and between centres. In the unique setting of a specialist bone infection unit, we have studied a cohort of adults with musculoskeletal infection to describe patterns of prescribing and drug levels, in order to help inform and standardise clinical practice in this patient group.

Relationship between teicoplanin dose and trough serum level

In this study of 110 trough levels taken from 141 patients, 51% reached a target trough of ≥20 mg/l, suggested as a threshold for improved outcome by previous studies. In comparison, only 27% of all samples assayed by the reference lab in 1998 achieved this range. However, this latter group is less stringently clinically defined, and may also include patients with ‘non-severe’ infection. In our study, patients who received teicoplanin 600 mg once daily were statistically more likely to achieve trough levels of ≥20 mg/l than those treated with lower doses. Significantly lower levels were attained in men, a finding which is not explained by differences in body weight, renal function, or dose regimens.

Constraints and limitations of this study

Of 141 patients treated with teicoplanin, 31 did not have a trough level taken. This may be accounted for by a short duration of treatment with teicoplanin, missing patient data (e.g. lack of unique identifier), or omission. There was wide inter-patient variation in age, renal function and body weight in this cohort, and the analysis of these parameters is also limited by missing data.

The patients studied here were adults who were medically stable enough to be discharged to the community. Our results cannot be extrapolated to other populations—in particular, to patients with organ failure, to those with sufficient co-morbidity to require ongoing in-patient care, or to children under the age of 16. In these instances,
especially in patients with significant hepatic or renal impairment, and in the setting of extremes of body mass, other significant comorbidity, or marked physical frailty, our routine practice is still to consider dose modification guided by therapeutic drug monitoring. Additionally, our data do not extend to follow-up regarding outcome of treatment, for which longer-term prospective studies would be required.

Repeat levels were taken less frequently than expected, given that over half of our cohort had levels outside our reference range. This reflects the logistical constraints of waiting 6 days for stable serum levels to be reached, and by the turn-around time in sending sera to a reference lab, in patients who may have already completed a substantial part of their treatment with vancomycin in hospital.

Amending teicoplanin regimens and therapeutic drug monitoring schedules

Based on the current practice of a single additional loading dose, we delay taking trough levels until 6–8 days after initiation of therapy. Regimens incorporating additional loading doses may make an earlier level more reliable.16 As we develop an understanding of the levels attained with standard dose regimens in clinically stable adults, teicoplanin levels may increasingly be reserved for selected patients in whom there is a particular need to monitor closely.

A policy of routine use of 600 mg daily doses of teicoplanin must be offset against disadvantages and risks. Higher doses inevitably increase cost of treatment, which may be difficult to justify until clear benefits are widely confirmed. Larger doses may also make administration via the im route less practical. The emerging benefits of higher teicoplanin doses must also be balanced against the potential risk of increased toxicity, although side-effects in this cohort were not associated with higher doses, and there is limited published evidence of adverse effects of increasing dose.6,14,20

Teicoplanin may be used in combination with other antimicrobial agents (most commonly beta-lactams, quinolones, fusidic acid, or rifampicin), and synergistic combinations may potentially facilitate lower teicoplanin doses. However, most published data are limited to in vitro studies or to experimental animal models.21,22 Without time–kill curves using the patient’s infecting organism, indifference or antagonism with certain antibiotic combinations cannot be excluded. Combination regimens, particularly with rifampicin, have raised concerns about the potential for developing antibiotic resistance.23 In our unit, most patients with gram positive infection receiving teicoplanin are therefore not treated concurrently with other antibiotic agents. However, polymicrobial infection may necessitate combination therapy, and in this cohort, 14 patients had a gram negative component to their infection, and received directed gram negative therapy in addition to glycopeptide.

Teicoplanin resistance and MIC testing

Most commonly identified gram positive pathogens are teicoplanin susceptible. However, important exceptions include resistance in some species of coagulase negative staphylococci (particularly Staphylococcus epidermidis and S. aureus)24 Staphylococcus aureus (EMRSA-17, teicoplanin intermediate Staphylococcus aureus (TISA)), and vancomycin resistant enterococci (VRE) with the Van A genotype.

We routinely perform teicoplanin MIC testing of all coagulase negative staphylococci isolated in 2 or more sterile site samples. In a multi-centre UK study, 6.5% of coagulase negative staphylococci were teicoplanin resistant (defined as MIC &gt;4 mg/l).18 Previous laboratory data analysis in our centre (Boland, 2005, unpublished) identified teicoplanin resistance (using the same breakpoint) in 4.4% of 91 isolates of coagulase negative staphylococci in orthopaedic patients treated with iv antibiotics over the course of a year, and confirmed the absence of resistance to teicoplanin in S. aureus isolates locally, including MRSA.

Outcome of teicoplanin treatment

Assessing the clinical cure rate in patients with bone and joint infection treated with teicoplanin and investigating the impact of varying teicoplanin levels on treatment outcome were outside the remit of this study. However, a previous multi-centre study of bone and joint infection sites clinical cure in 82–90% of patients treated with outpatient teicoplanin.20 The effect of teicoplanin MIC on the success of treatment is not clearly elucidated, but previous attempts to correlate MIC with clinical outcome have found no significant relationship.25,26

Conclusions

Based on current standard dosing regimens, 49% of our cohort achieved teicoplanin levels below the suggested threshold of 20 mg/l for patients with serious gram positive infection. Increasing the daily dose from 400 mg to 600 mg statistically improves the chances of attaining these levels. In this study, there was no evidence of increased side-effects with higher doses, but larger cohorts are needed to increase confidence in this observation. These data provide a preliminary basis for suggesting that, in selected, clinically stable adults with bone and joint infection, clinicians should consider the use of teicoplanin doses of 600 mg once daily, with an additional loading dose on the first day.

Conflicts of interest

The authors have no conflicts of interest to declare.

Acknowledgements

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References


