The use and therapeutic drug monitoring of teicoplanin in the UK
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ABSTRACT
Teicoplanin dosage recommendations for specific infections have been modified in recent years. However, there was no significant increase in the proportion of pre-dose concentrations > 20 mg/L between 1994 and 1998 in samples sent for teicoplanin assay at the Regional Antimicrobial Reference Laboratory, Bristol, UK. A questionnaire on the use of teicoplanin and therapeutic drug monitoring (TDM) was sent to all UK National External Quality Assurance Scheme antibiotic assay users. Teicoplanin was widely used in the UK, although vancomycin was more popular as a choice of glycopeptide. Fewer than 25% recommended teicoplanin TDM during routine use, the main reasons being perceived lack of toxicity and lack of evidence for the use of teicoplanin TDM. Pre-dose concentrations < 20 mg/L were considered appropriate for treatment of bacteraemia caused by methicillin-resistant Staphylococcus aureus by 53% of those responding. Data sheet advice was relied upon more than TDM as an indication of therapeutic dosing. Microbiologists who mainly used vancomycin tended to perform more TDM and seek higher serum concentrations when using teicoplanin than those who preferentially used teicoplanin.

Keywords Bacteraemia, drug-monitoring, glycopeptides, Staphylococcus aureus, teicoplanin, therapy

INTRODUCTION
Knowledge of the relationship between serum concentrations of teicoplanin and its therapeutic effect has accumulated since its introduction to the UK market in 1991. The UK teicoplanin data sheet recommends that, for severe infection, pre-dose concentrations > 10 mg/L should be maintained (Aventis Pharma Ltd, West Malling, UK). The potential significance of minimum post-dose concentrations has been raised in a few studies [1,2], but these are not recommended in the data sheet. Recent studies and meta-analyses have indicated that doses higher than those recommended in the data sheet may be needed to achieve pre-dose concentrations > 20 mg/L for effective treatment of septic arthritis, Staphylococcus aureus endocarditis and possibly other deep-seated staphylococcal infections [3–6].

For most UK hospitals, teicoplanin therapeutic drug monitoring (TDM) entails reference laboratory referral, as only a few centres perform in-house assays for this antibiotic. Taking into account the relative lack of toxicity of teicoplanin at standard dosage, there is little indication to measure serum concentrations in non-severe infection, with the exception of a few particular patient groups, e.g., burns patients or intravenous drug abusers [7,8]. Hence teicoplanin TDM can be restricted, in most cases, to the management of serious infections when it is important to ensure adequate dosing.

The Regional Antimicrobial Reference Laboratory at Southmead Hospital (Bristol, UK) first offered an antibiotic assay service for teicoplanin in 1993. In the first year, 473 samples were analysed by fluorescent polarisation immunoassay, increasing to 2021 samples in 1999. It might be expected that published reports over recent years recommending higher dosages and higher
serum concentrations would be reflected in the values of serum concentrations assayed since the service was introduced. A retrospective study of serum samples sent to this Antibiotic Reference Laboratory for teicoplanin assay was carried out in 1999 to determine whether the changing recommendations were reflected in the values of serum concentrations [9]. Surprisingly, over the 4-year period 1994–98, there was only a minor increase in the mean value of pre-dose concentrations analysed from 14.5 mg/L to 16.9 mg/L (p < 0.05), with 23% of all initial pre-dose teicoplanin concentrations determined in 1994 being ≥ 20 mg/L, compared to 27% in 1998. The reason for the lack of marked increase in concentrations and the low proportion of pre-dose concentrations that were >20 mg/L was not clear. In order to answer this question, the current use of teicoplanin in the UK was investigated with regard to both dosage and TDM.

**MATERIALS AND METHODS**

A questionnaire, for completion by the consultant medical microbiologist, was sent in 1999 to all 241 medical microbiology hospital departments participating in the UK National External Quality Assurance Scheme for antibiotic assays. Information was collected on the use of teicoplanin, the preferred glycopeptide at each hospital (teicoplanin or vancomycin), and the reasons for preference. Further questions on dosing, use of assays, expected concentrations in given clinical circumstances and source of dosing advice were specific to teicoplanin. Simple statistical methods (chi-square test) were employed to determine any correlation between the preferred choice of glycopeptide and the selected dosage or use of TDM for teicoplanin.

**RESULTS**

Completed anonymised questionnaires were returned from 149 of the 241 centres. Responses from two microbiologists who had only received a checklist of four): familiarity with vancomycin (n = 6), cost (n = 5), efficacy concerns (n = 5), and difficulty with assay (n = 2). These were excluded completely from further analysis.

Of the 139 microbiologists using teicoplanin, 54 (39%) considered it their first-choice glycopeptide, 80 (57%) preferentially used vancomycin, four (3%) used both equally, and one gave no answer. Those preferring teicoplanin were asked to list their reasons (in their own words). The commonest responses given were ‘no need to measure levels’ (n = 34; 63%), ‘less toxic or nontoxic compared to vancomycin’ (n = 29; 54%), and ‘ease of administration’ (n = 26; 48%). Those who replied that vancomycin was the first-choice glycopeptide indicated their reasons (again using a checklist of up to four suggestions) as being ‘cost concerns’ (n = 58; 73%), ‘familiarity with vancomycin’ (n = 49; 61%), ‘easier to assay’ (n = 37; 46%), and ‘teicoplanin efficacy concerns’ (n = 40; 50%).

The group preferring vancomycin was then asked to list the clinical circumstances in which teicoplanin rather than vancomycin would be recommended; ‘outpatient or community use’ was the most popular indication, cited by 47 (59%) of all those responding. Other indications included ‘poor renal function’ (n = 30; 38%), ‘vancomycin allergy or side effects’ (n = 24; 30%), ‘poor or no intravenous access’ (n = 8; 10%), ‘use with other nephrotoxic drugs’ (n = 8; 10%), and ‘prophylaxis’ (n = 6; 8%). Other reasons given were: ‘haematology or oncology use’; ‘for enterococci or streptococci’; ‘vancomycin resistance’; ‘paediatrics’; ‘elderly’; ‘prolonged therapy’; ‘line infection’; and ‘if no central line access’ (each cited in fewer than six responses).

**Dose recommended to treat an adult with methicillin-resistant *Staphylococcus aureus* (MRSA) soft tissue infection**

It was expected that the description of ‘an average-sized adult male’ would be read as a patient of c. 70 kg body weight as represented in the standard UK data sheet advice, i.e., ‘Adult and elderly patients with normal renal function’. In response, 36 different dosage regimes were suggested for the management of soft tissue infection. Some answers included a loading dose regimen, usually one additional dose in the first 24 h. As this was not specifically asked for, it cannot be assumed that those who did not mention loading would not use it, so this has not been included in the analysis of responses. Maintenance doses varied widely from 200 mg
once-daily to ≥800 mg once-daily. In a few responses, the dose was given as dose/body weight, with the largest recommended dose being ‘6–10 mg/kg once-daily’. For ease of interpretation, maintenance doses (or the minimum dosage in a given range) were grouped as <400 mg once-daily, 400 mg once-daily, and >400 mg once-daily. The highest doses were recommended by centres that preferentially used vancomycin (Fig. 1).

Six responses to this question included mention of TDM being used to guide dosing. Five responses were qualified with the initial statement that teicoplanin would not usually be the antibiotic of choice in this scenario. Other responses, given without a dose recommendation, were: ‘only vancomycin would be used in this scenario’ (n = 1); ‘the data sheet would be used to select an appropriate dose’ (n = 2); ‘the pharmacy would give dosing advice’ (n = 1); and ‘not applicable to a children’s hospital’ (n = 2). One microbiologist replied that there was ‘no MRSA in the hospital’.

Use of TDM

TDM would be recommended by 30 (22%) of the respondents when using teicoplanin. Of these, five were centres that used teicoplanin frequently as the first-choice glycopeptide, 23 were centres where vancomycin was the preferred glycopeptide, and two were centres that used both equally.

In 99 (71%) centres, teicoplanin TDM was not recommended routinely; however, 47 of these responses were further qualified by a statement that TDM might be used occasionally in defined circumstances such as renal failure or in the treatment of endocarditis. Other responses were marked ‘not applicable’ or left blank.

The commonest reasons, when stated, for not recommending the use of teicoplanin TDM were: ‘toxicity not related to levels’ (n = 24; 24%); ‘not convinced levels useful or no data to support their use’ (n = 21; 21%); and ‘no assay on site or nearby’ (n = 9; 9%). Other reasons given included: ‘results not timely’ (n = 3); ‘wide therapeutic range’ (n = 2); ‘peak level occasionally useful’ (n = 1); ‘cost’ (n = 1); ‘don’t use teicoplanin monotherapy’ (n = 1); ‘if seriously ill would use vancomycin’ (n = 1); ‘if need assays would use vancomycin’ (n = 1); and ‘concentrations achieved by standard dosage should exceed MIC of organism’ (n = 1).

All those recommending TDM, whether routinely or occasionally (n = 77), reported assay of pre-dose serum samples. In addition, almost half would also assay post-dose concentrations, but none reported use of ‘random’ samples. On-site teicoplanin TDM was performed at 11 (13%) of the centres that responded. Other centres reported using assay services at Southmead Hospital, Bristol (n = 54), University College Hospital, London (n = 7), Mater Misericordiae Hospital, Dublin (n = 5), Newcastle Public Health Laboratory (n = 1), Belfast Royal Victoria Hospital (n = 1), and Southern General Hospital, Glasgow (n = 1).

Desirable serum concentrations

Respondents were asked to indicate the teicoplanin serum concentrations that they considered desirable for the treatment of MRSA cellulitis, osteomyelitis, and bacteraemia. Almost all responses gave recommended pre-dose rather than post-dose concentrations. Two responses indicated only peak concentrations for each case (of 25–60 and 20–30 mg/L, respectively). No pre-dose or post-dose concentration >60 mg/L was recommended in any response. Responses were grouped according to the minimum acceptable concentration indicated where a range of acceptable concentrations was given, and further subgrouped according to the glycopeptide of choice. Responses from two centres with no glycopeptide preference were excluded. Acceptable pre-dose concentrations for MRSA cellulitis ranged from <10 mg/L to >20 mg/L (Fig. 2).
Peak concentration recommendations were also included in five responses. As with the responses for MRSA osteomyelitis and MRSA bacteraemia, there was a general trend towards a requirement for higher concentrations by those preferring to use vancomycin. However, on direct comparison of pre-dose concentrations of <20 mg/L and ≥20 mg/L, this trend did not reach statistical significance (p > 0.05).

Desirable pre-dose concentrations suggested for MRSA osteomyelitis were higher than for cellulitis (Fig. 3). A pre-dose concentration ≥20 mg/L was considered desirable by 54% of respondents. Peak concentrations in addition to troughs were indicated in six responses, and two other responses only stated peak concentrations (20–30 mg/L and 25–60 mg/L, respectively). One centre stated that it would not check concentrations in this situation, and other responses were unclear or marked not applicable.

In the third case scenario, recommended pre-dose concentrations for MRSA bacteraemia were similar to those for osteomyelitis (Fig. 4), with no microbiologist accepting a concentration <10 mg/L (n = 57). Pre-dose concentrations <20 mg/L were accepted by 25 (44%) of 57 respondents, but two of these stipulated that, for endocarditis, the pre-dose concentration should be ≥20 mg/L. Thirty (53%) responses stated that pre-dose concentrations should be >20 mg/L, including four which stated that their response was specific for the treatment of endocarditis. Two microbiologists expected a minimum pre-dose concentration of 30 mg/L. A further two responses indicated only post-dose concentrations, and nine included post-dose concentrations with the pre-dose recommendations. One centre stated that it would not use TDM in this circumstance, and four responses were unclear.

**Effect of assay results on dosing regimen**

If the teicoplanin assay demonstrated a concentration lower than anticipated, most (63; 81%) respondents stated that they would increase the dose, while five (6%) would maintain the same dose and re-assay. The proportions of each response were equally divided between the group preferring to use teicoplanin and the group preferring to use vancomycin. Six indicated that both options would be employed, and seven responded with ‘not applicable.’ ‘Other’ responses given included: ‘discuss with reference...’
laboratory’ (n = 1); ‘change antibiotic’ (n = 2); and ‘continue with twice-daily dose until levels acceptable’ (n = 2).

Source of guidance for teicoplanin dosing advice

The final question concerned the source that was relied on for an indication of therapeutic dosing for teicoplanin: the British National Formulary (BNF) or data sheet; assay results; or ‘other guidelines’. Overall, nearly half (49%) of all those responding (n = 111) used BNF dosing recommendations as the main indication of therapeutic dosing, 29 (26%) relied more on assay results, and 12 (11%) said that they would use both. Other responses included: ‘expert advice’ (n = 4); ‘literature/publications’ (n = 7); ‘own hospital recommendations’ (n = 4); and ‘clinical response’ (n = 3).

On comparison of the responses by first choice of glycopeptide, of those preferentially using teicoplanin (n = 40), 29 (73%) reported relying on BNF recommendations, while six (15%) relied more on assay results. In comparison, of those using mostly vancomycin (n = 60), 24 (40%) relied mainly on BNF recommendations when using teicoplanin, and 21 (35%) relied more on assay results (p < 0.01).

DISCUSSION

The present study reports on teicoplanin TDM practice in 149 UK hospitals, all of which participate in the UK National External Quality Assurance Scheme for antibiotic assays. It cannot be assumed that this represents the practice in all UK hospitals; microbiologists not using teicoplanin may have been less likely to return the questionnaire. However, the results may reflect overall trends.

Teicoplanin was widely used, but vancomycin was the first-choice glycopeptide in most responding hospitals. A small proportion of microbiologists do not recommend the use of teicoplanin at all. Cost concerns, followed by familiarity with vancomycin, appear to be the main reasons for vancomycin preference, while half of the vancomycin users indicated that they had concerns with the efficacy of teicoplanin. In contrast, perceived lack of need for assays and the lower toxicity of teicoplanin were most frequently cited as reasons by those favouring teicoplanin over vancomycin.

Familiarity with a particular drug may not always be a valid reason for selecting it, but there is certainly some evidence to demonstrate the superiority of vancomycin over teicoplanin monotherapy in some infections, e.g., severe staphylococcal infections [2,10–12]. The initial acquisition costs of teicoplanin are higher than those of vancomycin, although this may be offset in part by the nursing time required for administration of the vancomycin infusion and the cost of disposable equipment and assays. It has been suggested that the cost of using teicoplanin over longer courses of therapy is much closer to that of vancomycin [13], or even less when considering its use in the outpatient setting. This is now even more likely, as the cost of teicoplanin has recently fallen in the UK. The prolonged half-life of teicoplanin enables once-daily dosing, and some centres have reported alternate-day dosing for outpatient and home parenteral antibiotic therapy patients [14–17], securing its role in outpatient intravenous therapy as indicated by over half of the vancomycin users.

The nephrotoxicity of vancomycin is controversial. Certainly, it demonstrates greater nephrotoxic potential when combined with, for example, aminoglycosides than does teicoplanin [18–20]. Whether it is more nephrotoxic than teicoplanin when given as monotherapy is questionable [21,22]; however, ‘renal failure or impairment’ was cited as a reason for recommending teicoplanin by nearly 40% of those who would usually use vancomycin.

An important pharmacodynamic factor in effective treatment with teicoplanin has been shown to be the time for which the serum concentration remains above the MIC (T > MIC) [5]. Infrequent dosing is therefore feasible as long as serum concentrations do not fall below the MIC of the isolate (MIC < 4 mg/L) [23]. A relationship between outcome and maximum and minimum serum concentrations was found in one review of teicoplanin trials, but there was no direct correlation between dose and outcome [5]. There is no evidence in vitro of concentration-dependent killing when large doses are used [24,25]. Ideally, TDM would incorporate all patient, pharmacokinetic and pharmacodynamic factors to reach the optimum dosage regimen for each patient infected by a specific organism. Using standard
target concentrations for all patients is therefore a simplistic method of optimising dose regimens, but one that is much more accessible and manageable than, for example, applying population pharmacodynamic or pharmacokinetic modelling data to each patient.

The perceived lack of need for teicoplanin TDM in centres that use teicoplanin most frequently is interesting. For mild-to-moderate infection, there is little evidence to support its use unless abnormal renal clearance is anticipated, e.g., in intravenous drug abusers or renally impaired patients [8,26]. In severe infection, including joint infection and endocarditis, the relationship between outcome and pre-dose teicoplanin concentration is well-documented [3–5,27]. It has been shown that, for staphylococcal endocarditis and septic arthritis, a pre-dose concentration > 20 mg/L is associated with improved outcome [28,29]. The fact that two-thirds of those who mainly use teicoplanin state that the lack of need to perform TDM is a major advantage is therefore surprising. Considerable inter-individual variability in the serum concentrations of patients given the same doses of teicoplanin has been demonstrated [12,30]. Furthermore, at the time of the survey, the teicoplanin assay service was provided free of charge, so the cost implications were minimal. Teicoplanin data sheet recommendations may be considered somewhat conservative with respect to treatment of severe infection. As discussed, there is evidence to indicate that pre-dose concentrations > 20 mg/L are required for efficacy in some infective conditions, and some authors have even recommended concentrations > 30 mg/L [3].

Maintenance doses of 200–400 mg may be adequate for soft tissue infection, but higher doses are needed to attain pre-dose concentrations > 20 mg/L [31]. The wide range of dose recommendations for the treatment of MRSA cellulitis reported in question 3 suggests that there is no overall consensus about teicoplanin dosage for mild-to-moderate infection. However, this is also likely to be true for the management of mild infection with any other antibiotic. Those using vancomycin much more frequently than teicoplanin recommended the highest doses of teicoplanin, i.e., > 400 mg. This could be attributed to unfamiliarity with the dosing schedules, or with teicoplanin itself, but is more likely to reflect the ‘efficacy concerns’ indicated by over half of those preferring to use vancomycin. It was also interesting to note that, of all respondents who stated that they would recommend teicoplanin TDM, the majority were those who preferentially used more vancomycin. These vancomycin users also recommended higher mean pre-dose teicoplanin concentrations for each of the three clinical scenarios. Again, this may reflect personal concerns with efficacy at standard dosage, but could also indicate a greater familiarity with more recent publications of teicoplanin dosage recommendations. It may also explain why the cost of using teicoplanin (at higher doses) is a concern for many vancomycin users.

As anticipated, increases in the ranges and mean pre-dose concentrations suggested for MRSA cellulitis, osteomyelitis and bacteraemia, respectively, were observed. In many cases, the responses appeared to reflect either BNF or data sheet advice, or more recent publications (e.g., ≥ 10 mg/L or > 20 mg/L). In some responses, it was not clear whether acceptance of pre-dose concentrations < 10 mg/L or, as specifically stated in two responses, ‘> 18 mg/L’ or ‘> 22 mg/L’ was based on personal experience or some other evidence. Within the limits of reproducibility of the fluorescent polarisation immunoassay (10% error margin), a sample containing 20 mg/L teicoplanin might be reported as having a concentration between 18.0 mg/L and 22.0 mg/L. It is therefore unlikely that aiming for a minimum pre-dose concentration of specifically 18 mg/L or 22 mg/L on TDM will effect a significant difference in outcome when compared with 20 mg/L. A concentration of < 10 mg/L may be quite appropriate for mild infection, but it is questionable whether assays must be performed at all in these cases. The minimum pre-dose concentrations suggested for S. aureus bacteraemia varied from ≥ 10 mg/L to > 30 mg/L. Four responses stated that concentrations > 20 mg/L were required for the specific treatment of endocarditis, and there is evidence to show that concentrations maintained above 20 mg/L improve outcome for staphylococcal endocarditis. Teicoplanin is not recommended in the current UK guidelines for the treatment of staphylococcal endocarditis [32]. However, endocarditis may complicate up to 10–60% cases of S. aureus bacteraemia [33], so there is logic in maintaining concentrations > 20 mg/L for all cases of S. aureus bacteraemia, particularly if community acquired, until endocarditis has been excluded [5].
When assay results indicate subtherapeutic concentrations, the common response is to increase the dose. Following a once-daily dosing regimen of 3 mg/kg (without loading), a teicoplanin steady-state concentration was reached by day 10 in healthy volunteers [34]. However, if, following a loading dose, the pre-dose concentration after 3–5 days is still subtherapeutic, it is appropriate to increase the dose. Prolonging the loading period, as suggested in two responses, to reach steady state rapidly has been described [35], and may be a useful approach for severe infection when therapeutic levels must be reached immediately.

Finally, it was considered that the source of dosing advice might explain absence of a significant increase in serum concentrations over recent years. Overall, nearly half of those responding reported relying mainly on the BNF or data sheet as their indication of therapeutic dosing, i.e., using a maximum daily dose of 400 mg for adults weighing < 85 kg. Fewer than one-third reported relying mainly on results of serum assay to guide therapeutic dosing. A significantly higher percentage of those using teicoplanin in preference to vancomycin rely more on the BNF as their main dosing guide. Does this mean that those familiar with the use of teicoplanin feel comfortable with the efficacy observed using standard dosing and see no need to increase dosage? Other possible reasons for this difference have already been discussed. As this was an anonymous survey, it is not possible to comment on the individual hospitals represented in each response. It would be interesting to know whether those preferentially using teicoplanin, and particularly those using the more conventional doses, represent a different size of hospital and patient mix compared to those using higher doses (e.g., District General Hospitals vs. tertiary referral centres).

In conclusion, there has been no marked increase in the mean pre-dose teicoplanin concentrations assayed at the Regional Antibiotic Reference Laboratory at Southmead Hospital in recent years. Teicoplanin was widely used in UK hospitals, but was not the most popular ‘first-choice’ glycopeptide in those surveyed. There was a tendency towards lower mean dosage, less frequent assay and requirement for lower pre-dose concentrations by those who considered it their first-choice glycopeptide. Whether this was caused by lack of awareness, or acceptance of more recent evidence, or simply familiarity and acceptance of efficacy with teicoplanin at the doses used, was not known. The data sheet was still relied on more than assay results as an indicator of therapeutic dosing, but the proportion was significantly higher in the group that used teicoplanin most frequently. If the data sheet was updated to reflect the findings of recent studies, it would be interesting to observe what changes in the use of teicoplanin might follow. For example, would the teicoplanin users currently following data sheet guidance continue to use the dose they have experience of, increase the dose to observe new data sheet recommendations, or switch to using more vancomycin to avoid escalating drug acquisition costs, and start using TDM for vancomycin instead?

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REFERENCES


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