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Teicoplanin use in adult patients with haematological malignancy: Exploring relationships between dose, trough concentrations, efficacy and nephrotoxicity

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ABSTRACT

In 2010, our hospital introduced a higher target teicoplanin trough concentration of ≥20 mg/L by Day 3 for haematological malignancy patients. This study aimed to explore whether target trough concentrations were achieved, to identify factors associated with trough concentrations attained, and to assess clinical efficacy with teicoplanin treatments and nephrotoxicity. This was a retrospective, single-centre, cohort study of 172 teicoplanin treatments in 104 adults with haematological malignancy. Mixed-effects regression was used to evaluate factors affecting trough concentrations, and logistic regression was used to assess the relationship between trough concentrations and treatment outcomes. Nephrotoxicity was assessed using the RIFLE criteria. Considerable variability in trough concentrations was observed, with trough concentrations ≥20 mg/L rarely achieved early in therapy. A mixed-effects regression model explaining 52% of the variation in trough concentrations was developed. Dose and day of therapy were positively associated with trough concentration, whilst estimated renal function and, interestingly, acute myeloid leukaemia diagnosis were negatively associated ($P < 0.05$). Results suggested a positive relationship between trough concentration and the likelihood of a favourable outcome for coagulase-negative staphylococcal central line-associated bloodstream infections. Elucidation of a specific target concentration requires further investigation. Teicoplanin was well tolerated renally. Findings suggest a risk of underexposure if conventional teicoplanin doses are used in haematological malignancy patients. Given the variability in trough concentrations observed, the identified factors affecting trough concentrations attained and the suggested link with clinical outcome, individualised initial dosing followed by therapeutic drug monitoring is recommended to ensure early adequate exposure in this vulnerable patient group.

1. Introduction

Teicoplanin plays a major role in the treatment of multiresistant Gram-positive infections in patients with haematological malignancy [1,2]. Comparative studies versus vancomycin have shown teicoplanin to be equally effective but better tolerated with a lower risk of nephrotoxicity [3]. Teicoplanin is therefore often the preferred choice for haematological malignancy patients, but specific dosage guidelines and a target trough concentration for this patient group have not yet been determined.

There is evidence that higher teicoplanin trough concentrations may benefit certain clinical settings, including infection in patients with haematological malignancy [1,4–6], with increased loading and maintenance doses suggested to achieve this [1,5–8]. The revised Summary of Product Characteristics (SmPC) for teicoplanin in 2014 reflects a trend for higher trough concentration requirements [9]. The current recommended minimum trough concentration to be achieved after completion of the loading regimen is 15 mg/L for most infections, and the dosage recommendation to achieve this is three loading doses of 400 mg (6 mg/kg) at 12-h intervals followed by a single daily dose of 400 mg. Increased

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loading, higher doses and higher trough concentrations are recommended for infective endocarditis as well as bone and joint infections [9]. In terms of toxicity, it is generally recommended to keep trough levels <60 mg/L, but there is limited evidence to support this concern [10].

In the last 20 years, the incidence of Gram-positive infections among cancer patients has increased considerably. This has been related to the administration of more potent cytotoxic chemotherapy regimens that induce more severe neutropenia as well as the widespread use of intravascular catheters that predispose neutropenic patients to bloodstream infections with skin colonising bacteria. Indeed, coagulase-negative staphylococci (CoNS) are the most common cause of bloodstream infections in cancer patients and these infections are almost always line-related [11]. As CoNS are usually only susceptible to teicoplanin, vancomycin and other newer antimicrobials, rising minimum inhibitory concentrations (MICs) in CoNS are a significant concern [12,13] and, coupled with the impaired ability of neutropenic patients to fight infection, make it important to achieve adequate drug exposure as quickly as possible. Achieving adequate antibiotic exposure in the first days of therapy may accomplish better infection eradication and improve treatment outcomes [14].

Several hydrophilic antibacterials have displayed altered pharmacokinetics in haematological malignancy [1,2,15,16] and the dosage of teicoplanin required to achieve a specific target concentration is difficult to predict. In 2010, based on evidence suggesting that conventional doses may be too conservative [1,2,7], our hospital (Tallaght Hospital, Dublin, Ireland) introduced higher than conventional doses and a higher target trough level for teicoplanin of ≥20 mg/L by Day 3 for patients with haematological malignancy. This retrospective study was conducted (i) to determine whether haematological malignancy patients were achieving target trough concentrations, (ii) to identify associations between dosage, patient factors and trough concentrations attained, (iii) to explore the relationship between teicoplanin treatment and clinical outcome and (iv) to identify any associated nephrotoxicity.

2. Methods

2.1. Patients

All teicoplanin-treated adult patients with haematological malignancy admitted to Tallaght Hospital between March 2010 and May 2012 were identified from pharmacy department dispensing records. Patients were excluded if renal replacement therapy was conducted during teicoplanin therapy or if teicoplanin therapy was for <48 h.

2.2. Data collection

Information was collected from hospital records for each of the identified treatment episodes. Data collected included: demographics; medical history; clinical information associated with the treatment; haematology and biochemistry data; details of teicoplanin therapy and therapeutic drug monitoring (TDM); concurrent drug therapy; and microbiological and infection details. Creatinine clearance (CL_{Cr}) was calculated using the Cockcroft–Gault equation based on ideal body weight (IBW) [17]. IBW was calculated using the Devine equation [18]. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated Modification of Diet in Renal Disease equation [17]. Body surface area (BSA) was calculated using the Mosteller equation [19].

2.3. Teicoplanin treatment

Teicoplanin was administered by intravenous bolus injection. Hospital dosing policy was 600 mg (or 800 mg if body weight >80 kg) and the standard regimen was three loading doses at 12-h intervals followed by once-daily maintenance dosing. However, prescribed dosing regimens were at the discretion of treating physicians and hospital policy was not always followed.

2.4. Serum teicoplanin trough concentrations

Teicoplanin trough samples were taken immediately pre-dose as per hospital policy. The time of sample collection was reconciled with the time of the previous dose recorded on the medical chart, and only trough concentrations taken from 20 to 26 h post-dose were considered for inclusion in the analyses.

Serum teicoplanin concentrations were determined locally by fluorescence polarisation immunoassay using a TDX® analyser (Abbott Diagnostics Division, Maidenhead, UK). The quantification limit of the assay was 1.7 mg/L.

2.5. Antimicrobial susceptibilities

The antimicrobial susceptibilities of relevant Gram-positive organisms isolated from study patients were determined locally by broth microdilution using a VITEK® 2 system (bioMérieux UK Ltd., Basingstoke, UK) as per routine care. Isolates were reported as susceptible or resistant to teicoplanin in accordance with the current European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints [20]. Individual MICs for isolated pathogens were not available.

2.6. Analysis of factors associated with teicoplanin trough concentrations

Mixed-effects regression was conducted to establish the influence of patient factors on trough levels attained, with treatments nested in patients. Treatments were included in this analysis if there was a trough level taken 22–26 h post-dose on Days 3–7. In treatments with more than one trough level on Days 3–7, the first trough level was used. Treatments were excluded if the standard regimen of three loading doses every 12 h followed by a once-daily maintenance dose was not followed or if renal function was unstable.

Log teicoplanin trough concentration was used for the dependent variable as trough level data were positively skewed. Independent variables tested included: age; sex; total body weight (TBW); IBW; haematological malignancy diagnosis; dose; day of therapy; renal function using eGFR, both adjusted and unadjusted for BSA, and CL_{Cr}; C-reactive protein (CRP) level; serum albumin level; and white blood cell (WBC) and neutrophil counts. Mean values, calculated from Day 1 of teicoplanin therapy until the day of trough level measurement, were used for dose, renal function measures, blood counts, albumin levels and CRP levels.

2.6.1. Model development

Step-wise incorporation of patient covariates was conducted for model development. Variables that did not contribute to, or reduced the fit of, the model were removed sequentially and only significant variables were retained ($P < 0.05$). Evaluation of goodness-of-fit criteria (Akaike's Information Criterion and Schwarz's Bayesian Criterion) and the pseudo-R^2 afforded the final model. Pseudo-R^2, interpreted as the proportion of variance in trough level accounted for by the full model, was calculated by the formula: Pseudo-R^2 = [$\text{residual}_{(\text{null})} - \text{residual}_{(\text{full})}$]/$\text{residual}_{(\text{null})}$, where $\text{residual}_{(\text{null})}$ is the residual value