International Journal of Antimicrobial Agents xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Short Communication

Albumin concentration significantly impacts on free teicoplanin plasma concentrations in non-critically ill patients with chronic bone sepsis☆

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ARTICLE INFO

Article history:
Received 18 November 2014
Accepted 27 January 2015

Keywords:
Teicoplanin
Protein binding
Free
Hypoalbuminaemia
Population pharmacokinetics
TDM

ABSTRACT

The impact of decreased serum albumin concentrations on free antibiotic concentrations in non-critically ill patients is poorly described. This study aimed to describe the pharmacokinetics of a high-dose regimen of teicoplanin, a highly protein-bound antibiotic, in non-critically ill patients with hypoalbuminaemia. Ten patients with chronic bone sepsis and decreased serum albumin concentrations (<35 g/L) receiving teicoplanin 12 mg/kg 12-hourly intravenously for 48 h followed by 12 mg/kg once daily were enrolled. Surgical debridement was performed on Day 3. Samples of venous blood were collected pre-infusion and post-infusion during the first 4 days of therapy. Total and free teicoplanin concentrations were assayed using validated chromatographic methods. The median serum albumin concentration for the cohort was 18 (IQR 15–24) g/L. After 48 h, the median (IQR) free trough (fC_{min}) and total trough (tC_{min}) concentrations were 2.90 (2.67–3.47) mg/L and 15.54 (10.28–19.12) mg/L, respectively, although trough concentrations declined thereafter. Clearance of the free concentrations was significantly high relative to the total fraction at 38.6 (IQR 29.9–47.8) L/h and 7.0 (IQR 6.8–9.8) L/h, respectively ($P < 0.001$). Multiple linear regression analysis demonstrated that whereas total teicoplanin concentration did not impact on free concentrations ($P = 0.174$), albumin concentration did ($P < 0.001$). This study confirms the significant impact of hypoalbuminaemia on free concentrations of teicoplanin in non-critically ill patients, similar to that in critically ill patients. Furthermore, the poor correlation with total teicoplanin concentration suggests that therapeutic drug monitoring of free concentrations should be used in these patients.

1. Introduction

It has become increasingly clear that the free (unbound) antibiotic concentration is responsible for the pharmacological effect and a better understanding of this can enhance the accuracy of therapy and potentially improve clinical outcomes [1]. This might be of particular relevance for highly protein-bound antibiotics such as teicoplanin (90–95% bound), especially in critically ill patients where hypoalbuminaemia is frequent and as a consequence the volume of distribution (V) and clearance (CL) of the unbound drug are increased [2]. These pharmacokinetic (PK) changes could result in suboptimal teicoplanin exposures and may necessitate dose adjustments to ensure that therapeutic exposures are achieved [2]. In this regard, Mimoz et al. utilising a high-dose regimen [12 mg/kg every 12 h (q12 h) for 48 h, followed by 12 mg/kg once daily] in critically ill

☆ Data from this study were partially presented at the 32nd International Symposium on Intensive Care and Emergency Medicine, 20–23 March 2012, Brussels, Belgium [In: Meeting Abstract *Critical Care* 2012;16(Suppl 1):P69].

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http://dx.doi.org/10.1016/j.ijantimicag.2015.01.015
0924-8579/

patients with ventilator-associated pneumonia and severe hypoalbuminaemia (median albumin concentration 16.1 g/L) observed variations in the free fraction of teicoplanin ranging from 8% to 42%, but unfortunately did not correlate these with serum albumin concentrations [3].

This highlights three important shortcomings of available data on the pharmacokinetics of unbound teicoplanin. First, unbound concentrations are often not measured either clinically or for academic reasons [4]. Second, in the rare circumstances that unbound concentrations are determined, patients generally have not had serum albumin concentrations that were sufficiently low to alter the free teicoplanin pharmacokinetics significantly [5]. Third, no PK data are available describing the effect of hypoalbuminaemia on unbound concentration when using dosing regimens for non-critically ill patients with 'deep-seated' infections such as those of bone and prostheses, where the target total trough concentration (tC_{min}) is ≥20 mg/L [6,7]. One study did correlate clinical outcome and teicoplanin tC_{min} in patients ($n = 35$) with bone, joint and vascular-access infections treated with a high-dose regimen, but albumin concentrations were not determined [8]. Another study with a large cohort of bone and joint infections, which was designed to develop dosing guidelines for teicoplanin in the outpatient setting, also used a high-dose regimen but measured total trough concentrations rather than free concentrations in patients with normal albumin concentrations [4].

Data from the critical care literature suggest that hypoalbuminaemia is likely to alter teicoplanin pharmacokinetics significantly and, in particular, free concentrations [6]. To address the above deficiencies in the literature, we aimed to investigate the impact of decreased serum albumin concentrations on free teicoplanin concentrations in non-critically ill patients using a high-dose teicoplanin regimen for chronic osteomyelitis or septic arthritis.

2. Patients and methods

This single-centre, prospective, open-label, post-authorisation study was performed at Milpark Hospital, a private referral hospital in Johannesburg, South Africa. Ethical approval was obtained from the local ethics committee of Milpark Hospital. The study was conducted following the guidelines of the Declaration of Helsinki. Written informed consent was obtained either from the patient or, when appropriate, from their closest relative.

2.1. Selection of patients

Inclusion criteria were adult patients (aged >18 years) referred for surgical debridement of chronic, deep-seated, Gram-positive bone or joint infections with decreased serum albumin concentrations (<35 g/L; normal range 35–52 g/L) who at the discretion of the physician and/or orthopaedic surgeon were deemed to require high-dose teicoplanin (Targocid®; Sanofi-Aventis, Midrand, South Africa) regimens for ≥4 days (loading dose of 12 mg/kg q12 h intravenously for 48 h, followed by 12 mg/kg once daily over 30 min). Only patients who had debridement performed on Day 3 of antibiotic therapy were enrolled. Patients who were acutely ill, had suspected glycopeptide allergy, were pregnant or who had moderate-to-severe renal dysfunction [arbitrarily defined as an estimated glomerular filtration rate (eGFR) <59 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease (MDRD) equation for GFR calculation] were excluded from enrolment. Chronicity of osteomyelitis or septic arthritis was defined as duration of >4 weeks. Hypoalbuminaemia was defined as a serum albumin level <25 g/L [2]. Demographic characteristics were recorded at recruitment and during the 4-day study period. Urine creatinine concentrations were not measured.

2.2. Blood sampling

The investigations took place during the first 4 days of therapy. Samples were collected 15 min before and 30, 120 and 720 min after each teicoplanin administration. Following centrifugation at 3000 rpm for 10 min at 4 °C, plasma was removed and transferred into separate tubes. Two fractions were kept frozen at −20 °C whilst being transferred to the Ampath National Reference Laboratory (Centurion, South Africa) for analysis of total and free concentrations. The other three tubes were used for onsite measurement of biochemistry and biomarkers.

2.3. Drug assay

Plasma teicoplanin concentrations were determined at the Department of Esoteric Sciences at Ampath National Reference Laboratory by a validated high-performance liquid chromatography (HPLC) method as described by Roberts et al. [6]. The non-protein-bound fraction of teicoplanin was determined by HPLC after filtration with a Centrifree® device [6]. Standards and controls were prepared in blank plasma. The assay had a linear range of 0.3–26.6 mg/L, a correlation coefficient (r^2) of 0.9984, a limit of detection of 0.40 mg/L and a limit of quantification of 1.36 mg/L. The accuracy (95% confidence level) was determined as 2.0 ± 0.2 and 20.0 ± 2.3 at the nominal concentration with a precision <5% coefficient of variation ($n = 10$).

2.4. Pharmacokinetic analysis

Non-compartmental PK analysis was performed using previously described methods [9]. The following covariates were evaluated for effects on free teicoplanin concentrations: total teicoplanin concentration; serum albumin concentration; age; MDRD creatinine clearance; and serum creatinine concentration. Following identification of significant covariates in univariate testing ($P < 0.2$), a multiple linear regression model was constructed to determine the primary determinants of subtherapeutic trough concentrations, which was defined as a total trough concentration (tC_{min}) <20 mg/L. Goodness of fit of the model was assessed by the Hosmer–Lemeshow statistic. All statistical analyses employed IBM SPSS Statistics for Windows v.19 (IBM Corp., Armonk, NY). A P-value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

Ten patients (eight male and two female) with confirmed Gram-positive, chronic, deep-seated bone or joint infections referred to Milpark Hospital for surgical debridement were recruited over a 4-month period. Their demographic data are given in Table 1. All patients had decreased albumin concentrations (<35 g/L) at recruitment. Despite two patients not actually having hypoalbuminaemia as per the definition of <25 g/L (i.e. concentrations of 27 g/L and 34 g/L), the median [interquartile range (IQR)] for the cohort was 18 (15–24) g/L. Small changes in serum creatinine concentrations occurred particularly perioperatively; on Day 3, the median value was 84.0 (65.5–106.0) μmol/L.

3.2. Pharmacokinetic profile

Teicoplanin free trough concentrations (fC_{min}) and tC_{min} over the 4-day study period are given in Table 2. After 48 h, the

Please cite this article in press as: Brink AJ, et al. Albumin concentration significantly impacts on free teicoplanin plasma concentrations in non-critically ill patients with chronic bone sepsis. Int J Antimicrob Agents (2015), http://dx.doi.org/10.1016/j.ijantimicag.2015.01.015