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BRIEF REPORT

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Steady-state trough serum and epithelial lining fluid concentrations of teicoplanin 12 mg/kg per day in patients with ventilator-associated pneumonia

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Abstract *Objective:* To determine the steady-state trough serum and epithelial lining fluid (ELF) concentrations of teicoplanin 12 mg/kg per day in critically ill patients with ventilator associated pneumonia. *Design and setting:* Prospective, pharmacokinetic study in the surgical intensive care unit in a university hospital. *Patients:* Thirteen adult patients with nosocomial bacterial pneumonia on mechanical ventilation were enrolled. *Interventions:* All subjects received a 30-min intravenous infusion of 12 mg/kg teicoplanin every 12 h for 2 consecutive days followed by 12 mg/kg once daily. Teicoplanin concentrations in serum and ELF were determined simultaneously 4–6 days after antibiotic administration started. *Measurements and results:* The median total and free concentrations of teicoplanin in serum at trough were 15.9 μg/ml (range 8.8–29.9) and 3.7 (2.0–5.4), respectively. The concentration in ELF was 4.9 (2.0–11.8). *Conclusions:* In critically ill patients with ventilator-associated pneumonia the administration of high teicoplanin doses is required to reach sufficient trough antibiotic concentrations in lung tissues at steady state. At that time trough-free concentrations of teicoplanin in serum and ELF are comparable.

Keywords Teicoplanin · Lung diffusion · Epithelial lining fluid · Intensive care unit · Human

Introduction

Ventilator-associated pneumonia is the second source and the first cause of death from nosocomial infections in critically ill patients [1]. Although the introduction of new antimicrobial therapy has substantially improved the outcome of these infections, there are a number of cases in which antimicrobial therapy fails to be effective, particularly when only suboptimal concentrations of antibiotics are attained at target site [2].

Teicoplanin is a glycopeptide antibiotic which is marketed for the treatment of ventilator-associated pneumonia caused by resistant Gram-positive bacteria [3]. Teicoplanin concentrations have been determined in whole lung tissue, sputum, respiratory secretions and pleural fluid [4]. However no investigation has examined in epithelial lining fluid

(ELF), which has been advocated as more reliable since infections develop mainly in extracellular spaces [5].

Glycopeptides do not show significant concentration-dependent killing across the range of concentrations likely to be observed in human dosing [6]. Saturation of the killing rate occurs at low multiples of the minimal inhibitory concentration (MIC), usually around four to five times the MIC. Concentrations above these values do not kill the micro-organisms any faster or more extensively. Thus the extent of killing in this pattern of bactericidal activity is largely dependent on the time of exposure. Therefore clinical efficacy is correlated better with trough (predose) rather than peak antibiotic concentrations. The susceptibility breakpoint for teicoplanin is 4 μg/ml. Current recommendations suggest trough concentrations in serum be maintained above 20 μg/ml [7] due to the sustained decrease in Gram-positive cocci susceptibility to glycopeptides observed during the past decade [8]. Achieving such concentrations in healthy volunteers requires a daily teicoplanin dose of 12 mg/kg [7, 9]. However, no study has been conducted in critical care patients to support this dosing regimen.

Teicoplanin is extensively bound to serum proteins, mainly albumin, the free fraction being 6–12% irrespective of serum concentration [10]. Teicoplanin protein binding is likely to be altered in ICU patients, either due to the decrease in albumin level and/or to interactions with other drugs sharing the same binding sites. Because only unbound drug may distribute within tissues, total serum concentration is not an ideal parameter for rational dosing of antibiotics, especially for those compounds with extensive protein binding [11]. Moreover in vitro MIC values are determined using free antibiotic concentrations, and unbound serum concentrations are responsible for its antimicrobial activity [11]. Therefore unbound trough concentrations of teicoplanin at steady state should be more relevant than the corresponding total serum concentration to predict clinical outcome.

Therefore we conducted a study to estimate the steady-state trough serum (total and free) and ELF concentrations of 12 mg/kg teicoplanin administered twice daily during the first 2 days and then once daily to critically ill patients with ventilator-associated pneumonia.

Patients and methods

The study was approved by our local ethics committee (CCPPRB de la region Poitou Charentes, protocol no. 04.05.15). Prior to inclusion in the study all patients or their closest relative provided written informed consent after adequate information.

Selection of patients

Adult patients hospitalized in the ICU for at least 48 h prior to diagnosis were considered eligible for inclusion in the study when presumed to have ventilator-associated pneumonia due to Gram-positive cocci. Thirteen subjects (11 men and 2 women) completed the study; their characteristics are presented in Table 1. Pneumonia was suspected in the presence of a persistent and new radiographic infiltrate associated with purulent tracheal secretions, fever above 38.5°C or hypothermia below 36.5°C, and leukocytosis at 12,000 cells/mm^3 or leukopenia at 4,000 cells/mm^3. Pulmonary specimens for quantitative microbiological cultures were obtained using a plugged telescoping catheter (Combicath, Plastimed, St-Leu-La-Forêt, France), and the diagnosis of pneumonia was established when the number of growing bacteria was above the standard cutoff value of 1,000 colony-forming unit per milliliter [12]. Patients were excluded from the study if they were known or suspected allergic to teicoplanin or another glycopeptide, received teicoplanin during the 15 days prior to the study, exhibited renal dys-

Table 1 Patients' characteristics. Data are expressed as median and range in parentheses unless otherwise indicated

Age (years)	61 (18–83)
Gender: M/F *n*	11/2
Weight (kg)	83 (67–111)
Height (cm)	175 (155–187)
SAPS II on admission	38 (23–68)
Main diagnosis on admission *n*	
Polytrauma	9
Cranial trauma	1
Severe acute pancreatitis	2
Abdominal surgery	1
Time between admission and inclusion (days)	6 (4–14)
SAPS II at inclusion	34 (17–67)
Albumin level in serum at inclusion (g/l)	16.1 (14.2–28.4)
Estimated creatinine clearance[a] at inclusion (ml/min)	113 (65–217)
Time between inclusion and BAL (days)	4 (4–6)
Estimated creatinine clearance[a] at BAL (ml/min)	114 (61–204)
Time between BAL and the last teicoplanin dose (h)	20 (18–24)

[a] Using the Cockcroft and Gault [13] formula

function defined by an estimated creatinine clearance [13] of less than 60 ml/min, had a contraindication to the realization of a bronchoalveolar lavage (BAL) such as severe hypoxemia or significant coagulation abnormalities, or had pneumonia due at least one strain resistant to teicoplanin.

Teicoplanin administration, BAL, and blood sampling

Teicoplanin was administrated as a 30-min infusion of 12 mg/kg twice daily for 2 consecutive days, then once daily. Between days 4 and day 6 a blood sample was taken 18–24 h after the last teicoplanin dose to assess trough concentration of the drug. After centrifugation at 3,000 rpm for 10 min at 4°C, the serum was removed and transferred into four separate tubes. One fraction was kept frozen at 20°C until assayed. Another fraction was ultrafiltered with a Centrifree system (CF50A model, Amicon, Epernon, France) for determination of unbound concentrations. The other two fractions were stored for urea and albumin assays. BAL was performed simultaneously with blood sampling using a standardized procedure. Briefly, a fiberscope was used to lavage a peripheral lung subsegment rapidly with two syringes of 20 ml sterile saline. The first aspirate was removed. The second was immediately centrifuged at 3,000 rpm for 10 min at 4°C. The supernate was separated and stored in two aliquots for teicoplanin and urea assays. All BALs were performed by the same experienced physician.

Teicoplanin assay

The concentrations of teicoplanin in plasma and BAL were determined using solid-phase extraction with Oasis HLB (Waters, Saint Quentin en Yvelines, France) and liquid chromatography coupled with tandem mass spectrometry operating in the positive multiple reaction monitoring mode. Only the main component A_{2-2} was used for quantification. The calibration curve of the plasma assay was linear over a concentration range of 0.625 μg/ml (lower limit of quantification) to 40 μg/ml (correlation coefficient 0.992). The calibration curve of the BAL assay was linear over a concentration range of 0.05 μg/ml (lower limit of quantification) to 0.8 μg/ml (correlation coefficient 0.993). This range of concentrations was chosen because of the dilution factor induced by BAL when estimating teicoplanin concentrations in ELF (see below).

Calculation of teicoplanin concentrations in ELF

The concentration of teicoplanin in the ELF (Tei_{ELF}) was approximated as follows, using urea as an endogenous marker [14, 15, 16, 17]: $Tei_{ELF} = Tei_{BAL} \times Urea_{SER}/Urea_{BAL}$, where Tei_{BAL} is the measured concentration of teicoplanin in BAL fluid, $Urea_{SER}$ is the concentration of urea in serum, and $Urea_{BAL}$ is the concentration of urea in the BAL fluid.

Results

Teicoplanin administration and BAL procedures were well tolerated and no serious clinical or clinically significant biological adverse effects were observed. Micro-organisms responsible for pneumonia were *Staphylococcus aureus* ($n = 11$, including four methicillin-resistant strains) and *Streptococcus pneumoniae* ($n = 2$). Resolution of pneumonia was achieved in all patients after 14 days of therapy, and all left the ICU alive. Unbound teicoplanin concentrations in serum and ELF were above 2 μg/ml in all the patients. The fraction of teicoplanin unbound to

Table 2 Individual steady-state serum and epithelial lining fluid (ELF) concentrations at trough and percentage penetration of 12 mg/kg teicoplanin once daily administered to 13 critically ill patients with ventilator-associated pneumonia (*FU* fraction of teicoplanin not bound to plasma proteins)

Patient no.	Serum (μg/ml)			ELF (μg/ml)	Percentage penetration[a]
	Total	Free	FU (%)		
1	20.1	4.1	20	3.6	88
2	10.1	3.4	34	11.3	332
3	8.8	3.7	42	10.9	294
4	13.8	2.8	20	3.6	128
5	15.0	4.6	31	11.8	256
6	13.5	3.0	22	2.0	66
7	15.9	4.5	28	10.8	240
8	16.2	5.4	33	2.6	48
9	21.0	4.6	22	5.4	117
10	18.1	4.3	24	5.6	130
11	23.8	2.0	8	4.9	245
12	29.9	2.6	9	3.8	146
13	14.2	2.4	17	3.5	146
Median	15.9	3.7	22	4.9	146
Range	8.8–29.9	2.0–5.4	8–42	2.0–11.8	48–332

[a] ELF to free serum concentration ratio values

serum proteins ranged from 8% to 42%. Other relevant parameters are listed in Table 2.

Discussion

Many studies have been performed to assess ELF distribution of various antibiotics in patients with ventilator associated pneumonia. ELF distribution varied widely among compounds, with ELF to serum concentration ratio values at steady-state estimated at 20% for vancomycin [18] and ceftazidime [15], 60% for piperacillin [14], and 100% for cefepime and linezolid [16, 17]. Furthermore, with linezolid in healthy volunteers this ratio was reported to be equal to 300% in one study [19] and to 800% in another one [20]. There is no clear explanation for such a wide variability, but many factors including differences in sampling times, dosing regimens, and experimental uncertainty may have contributed. Important variability was also observed between the extreme values of the percentages of penetration determined individually in our study. Again, this can most likely be explained by experimental uncertainty, in particular due to the necessity of correcting measured concentrations by a dilution factor which is probably appropriately estimated on average but not necessarily within any particular individual.

Every patient was sampled predose, mainly because trough concentration of teicoplanin is a major predictor of treatment effectiveness [21]. However, as another advantage teicoplanin distribution equilibrium is likely to be attained making tissue to serum concentration ratios more relevant than when determined at early time postdose. Furthermore, for reasons noted above not only total but also unbound teicoplanin concentrations were assayed in serum. As a consequence measured concentrations were too low for being determined using the commercially available immunoenzymatic assay and a new LC-MS/MS: liquid chromatography-mass spectrometry/mass spectrometry method had to be developed, which was also more accurate and precise, to determine ELF concentrations.

The studied dosing regimen led to trough median teicoplanin concentrations in serum at steady-state equal to 15.9 μg/ml. This concentration is slightly lower than the expected target value of 20 μg/ml. However, because the unbound fraction of teicoplanin in these patients was much higher than expected, possibly due to a half decrease in albumin level in serum, the median unbound trough serum concentration of teicoplanin was equal to 4 μg/ml, which is above the value of 2 μg/ml corresponding to a target trough total serum concentration of 20 μg/ml, with an unbound fraction of only 10% [10]. Interestingly, median ELF and unbound serum concentrations of teicoplanin were close to each other.

Despite the use of high teicoplanin doses no clinical or clinically significant biological adverse events were reported in our small sample size study. Administration of multiples high teicoplanin doses up to 12 mg/kg in healthy volunteers or 15 mg/kg in patients is generally well tolerated [3]. Side effects are infrequent, mild, transient, and do not require treatment.

Conclusions

For antibiotics highly bound to serum proteins free concentrations should be preferred to total concentrations. The teicoplanin dosage tested in this study (12 mg/kg four times every 12 h followed by 12 mg/kg once daily) seems adequate for the treatment of ventilator-associated pneumonia due to Gram-positive cocci, as observed in our small sample size study. Another study including more patients is required to confirm the effectiveness of this dosing regimen.

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