Variability of protein binding of teicoplanin and achievement of TDM targets: Lessons from the DALI Study

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Background

Teicoplanin is a valuable antibiotic for infections caused by Gram positive bacteria including methicillin resistant Staphylococcus aureus (MRSA) although accurate dosing in critically ill patients may be complicated by altered pharmacokinetics. The aim of this study was to describe the variability in protein binding of teicoplanin in critically ill patients and to evaluate in what number of patients therapeutic target concentrations were achieved.

Materials and methods

Samples

- Blood samples were collected from critically ill patients included in the DALI[1] study, and receiving teicoplanin (n=13). Patients were recruited from 8 ICUs in Belgium, France, Greece and Spain.

Methods

- **Sampling:** blood samples were taken on one day at both the mid-point and the end of the dosing interval.
- **Data collection:** was conducted by trained staff at each participating centre and entered onto a case report form (CRF).
- **Analysis:** Total teicoplanin concentrations were assayed using a validated chromatographic method, including liquid/liquid extraction followed by reversed phase HPLC (Waters 2695 Alliance, X Bridge C18 2.5 µm 4.6 x 30 mm column, Waters, Milford, MA, USA) and UV detection (996 Photodiode array detector, Waters). Ultrafiltrates of plasma free Teicoplanin were prepared by equilibrating 500 µL of plasma at 37° C for 20 min in Amicon Ultra-4 regenerated cellulose 30,000 molecular weight cut-off centrifugal filter devices (Millipore, Billerica, USA) before centrifugation at 3040×g for 20 min at 37° C. The ultrafiltrate was then transferred to autosampler vials and 50 µL was injected directly into the HPLC system described above. UV detection was at 210 nm.
- **Therapeutic ranges:** lower therapeutic range of teicoplanin was defined as total trough concentrations from 10-20 mg/L and the higher range as 10-30 mg/L (for deep-seated infections).

Results

Patient characteristics and pharmacokinetic parameters are shown in Table 1 and 2.

Table 1 Patient characteristics

	n	Median	IQR	Range
No. of patients	13			
Male/Female	7 / 6			
Age (years)		58	41 – 69	24 – 75
Body Weight (kg)		80	72 – 90	40 -115
Dose (mg)				
1600mg – 24h	1			
600mg – 24h	1			
400mg – 12h	6			
400mg – 24h	4			
400mg – 48h	1			
Dose/kg/day (mg/kg/day)		8.0	5.3 – 8.9	2.7 – 20.0
Dose/kg (mg/kg)		5.3	4.4 – 7.7	3.5 – 17.8
Serum creatinine concentration (mg/dL)*		0.98	0.67 – 1.20	0.42 – 2.14
Estimated GFR (mL/min)*		71	38 – 94	25 – 167
Serum albumin concentration (g/L)**		28	21.5 – 29.5	17.5 – 34
APACHE II score		24	17 – 30	3 – 38
SOFA score		8	4 – 10	2 – 16

Abbreviations : IQR: Interquartile Range ; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment

* exclusion of 3 patients with continuous renal replacement therapy; ** no data available from 2 patients.

Table 2 Pharmacokinetic parameters

	Median	IQR	Range
Total teicoplanin			
Mid dose (mg/L)	13.6	11.2 – 26.0	5.2 – 49.5
Trough (mg/L) §	11.85	10.2 – 22.7	4.3 – 40.5
AUC (mg/L x h^{-1}) §	398	318 – 798	162 – 6886
T1/2 (h) §	31.3	19.1 – 43.5	13.5 – 88.2
CL (mL/min/kg) §	0.3	0.1 – 0.5	0.02 – 0.57
Vd (L/kg) §	0.8	0.4 – 1.1	0.16 – 1.36
Free serum teicoplain (mg/L)			
Mid dose	1.5	0.7 – 2.5	<0.1 – 10.0
Trough §	1.8	0.6 – 2.6	0.1 – 4.5
Fraction unbound teicoplanin (%)			
Mid dose	6.9	4.5 – 15.6	<0.7 – 28.9
Trough §	8.2	5.5 – 16.4	3.0 – 28.6

Abbreviations: AUC: area under the concentration-time curve; CL: total body clearance; T1/2: half-life; Vd: volume of distribution.

§: no data from 1 patient.

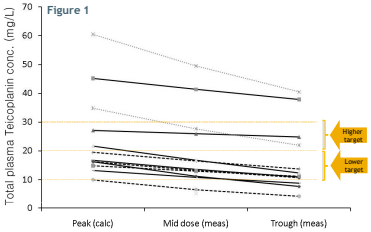
Total Teicoplanin target attainment

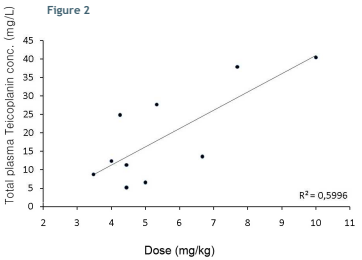
Total C_{trough} of 10 mg/L was attained in 4 of 6 patients (at day 1-2), in 3 of 4 patients (at day 5-11) and 2 of 3 patients (steady state, > 14 days), respectively. Only 42% of patients had total trough concentrations between 10-20mg/L while 58% had total trough concentrations between 10-30 mg/L. Two patients (17%) had trough concentrations > 30 mg/L (Figure 1). Total teicoplanin concentrations correlated with dosage. Based on our data, a dosage of at least 5 mg/kg was necessary to obtain a total C_{trough} of 10 mg/L (data not shown). In Figure 2, selected patient results (n=10) are included, showing a correlation with ρ = 0.77 (p=0.0083) between teicoplanin levels at 12h post-dosing for a given dose of 400mg and the dose/kg.

Results

Figure 1 Teicoplanin plasma concentrations for all patients at given time points. Peak (calc) concentrations are calculated using PharMonitor. Mid-dose and Trough (meas) concentrations are measured concentrations. Solid line: patients monitored during D1-2. Dashed line: patients monitored during D5-11. Grey dotted line: Patients monitored during steady state (SS).

Figure 2 Relationship between dose/kg (with a given dose of 400mg) and plasma teicoplanin concentration 12 hours post dosing. The solid line is least fit to the data. Pearson correlation coefficient of 0.77 (p=0.083)

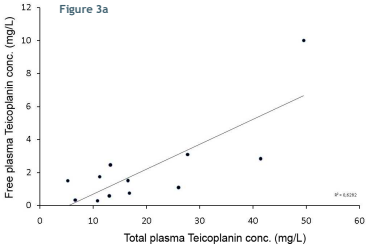




Free plasma teicoplanin concentration

Free plasma teicoplanin levels ranged between 0.3 and 10 mg/L (mid dose) and 0.1 and 4.5 mg/L (trough), respectively. The correlation between total and free antibiotic concentrations for the mid-point and trough concentrations was moderate (ρ = 0.79, p=0.0021, Figure 3a and ρ = 0.63, p=0.027, Figure 3b, respectively). The impact of plasma albumin concentrations on the free teicoplanin fraction is shown in Figure 4. High inter-patient variation is found, with higher free fractions seen in patients with lower albumin levels (Spearman's ρ = 0.56, p=0.0078).

In patients without hypo-albuminemia, a protein binding of teicoplanin of 90% is generally accepted. Consequently, we can hypothesize that the lower therapeutic range of free plasma teicoplanin should be in the range 1-2 mg/L (trough concentration). In our patient population, in 4 of the 12 patients (33%) free C_{trough} target attainment was not predictable based on the total C_{trough} target attainment (Table 3). Also the use of a published prediction model that takes into account the albumin concentration[2], resulted in only a moderate correlation between measured and calculated free concentrations (ρ = 0.63, p=0.003)



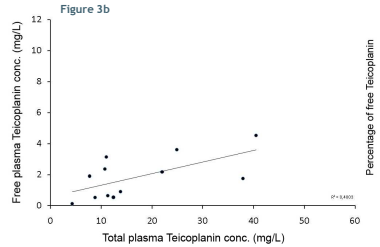


Figure 3 Relationship between free and total teicoplanin concentration for mid-dose (a) and trough (b) plasma samples. The solid line is least fit to the data. Pearson correlation coefficient of 0.79 (p=0.0021) (a) and 0.63 (p=0.027) (b).

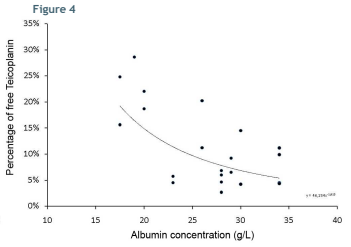


Figure 4 Impact of plasma albumin concentrations on the percentage of free teicoplanin. Both mid-dose and trough samples are included in the plot. Spearman's coefficient of rank correlation of -0.56 (p=0.0078).

Table 3 Cross tab analysis: free C_{trough} target attainment versus total C_{trough} target attainment.

	Total C_{trough} ≥ 10 mg/L	Total C_{trough} < 10 mg/L
Free C_{trough} ≥ 1 mg/L	6	1
Free C_{trough} < 1 mg/L	3	2

Conclusion

- Teicoplanin concentrations were highly variable.
- The variability of teicoplanin protein binding is very high in critically ill patients, placing significant doubt on the validity of total concentrations for TDM.
- Free plasma teicoplanin concentrations depend on albumin concentrations, but are difficult to predict via algorithms.
- Directly measured free plasma concentrations might be a more reliable guide in the selection of the optimal drug dose.

References

[1] Roberts, J.A., De Waele, J.J., Dimopoulos, G., Koulenti, D., Martin, C., Montravers, P., Rello, J., Rhodes, A., Starr, T., Wallis, S.C., et al. 2012. DALI: Defining Antibiotic Levels in Intensive care unit patients: a multi-centre point of prevalence study to determine whether contemporary antibiotic dosing for critically ill patients is therapeutic. BMC Infect Dis 12:152.
[2] Yano, R., Nakamura, T., Tsukamoto, H., Igarashi, T., Goto, N., Wakiya, Y., and Masada, M. 2007. Variability in teicoplanin protein binding and its prediction using serum albumin concentrations. Ther Drug Monit 29:399-403.

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