The impact of vancomycin protein binding on target attainment in critically ill children

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Background

Critically ill patients in particular exhibit marked variability in plasma protein levels, which may lead to altered drug pharmacokinetics (PK) and -dynamics (PD).

Objectives

The objectives of this study were to investigate vancomycin plasma protein binding and evaluate target attainment rates, using different PK/PD targets, in critically ill children.

Methods

Thirty-two paediatric intensive care patients, in whom intravenous intermittent (ID, 15mg/kg q6h) or continuous (CD, loading dose 15mg/kg; maintenance dose 40mg/kg q24h) dosing with vancomycin was indicated, were included. Blood samples were collected during first and/or assumed steady-state (ID) and minimum 12h after start of vancomycin infusion (CD). Bound and unbound drug were separated, after incubation (30 minutes, 37˚ C), using a validated ultrafiltration method (1885g, 30 minutes, 37˚ C). Total and free vancomycin concentrations were measured using a validated chemiluminescence microparticle immunoassay technique (Architect i2000SR Plus analyzer, Abbott diagnostics, Illinois, US). Evaluated PK/PD targets included Area Under the concentration-time Curve (AUC) over 24h in steady-state conditions divided by the Minimal Inhibitory Concentration (MIC) of the suspected pathogen (presuming a MIC of 1 mg/L) >= 400, freeAUC/MIC >= 200, total trough concentration between 10-15 mg/L (ID) and total concentration between 20-25 mg/L (CD). (f)AUC was calculated using a non-compartmental analysis based on the log-linear trapezoidal rule with PK Solver (Microsoft Office Excel version 2013). Covariates on free vancomycin concentrations and free fraction were tested using a linear mixed model analysis using SPSS Statistics version 22 (IBM, New York, USA).

Results

Demographic characteristics	Value[a]
Male/Female	18/14 (56/44)
Age (years)	4.1 (1.3-6.3)
Weight (kg)	17 (10-23)
Clinical characteristics	Value[a]
Empirical start	21 (66)
Albumin concentration (g/L)	30.6 (26.9-33.8)
Total protein concentration (g/L)	55.8 (49.8-60.9)
Total vancomycin concentration (mg/L)	16.6 (8.7-30.3)
Free vancomycin concentration (mg/L)	12.2 (6.2-21.7)
Free vancomycin fraction (%)	71.1 (65.5-79.7)
Treatment and sampling characteristics	Value[a]
Intermittent dosing (n=29 patients)	
Number of samples	176 (97)
Collected samples per dose	5 (4-5)
Continuous dosing (n=3 patients)	
Number of samples	6 (3)
Collected samples per patient	2 (2-2)
Target attainment results	Value[a]
Number of calculated (f)AUC/MIC	24
AUC/MIC	425 (293-497)
fAUC/MIC	294 (222-357)
AUC/MIC >= 400	13 (54)
fAUC/MIC >=200	20 (83)
Intermittent dosing	
Number of trough samples	32
Total trough concentration (mg/L)	6.7 (4.7-8.7)
Total trough concentration > 10-15 mg/L	3 (9)
Continuous dosing	
Total concentration (mg/L)	14.5 (10.2-18.7)
Total concentration > 20-25 mg/L	0 (0)

Table 1: Demographic, clinical and treatment and sampling characteristics and PK/PD target attainment. [a]Values: median (InterQuartile Range) or No. (%).

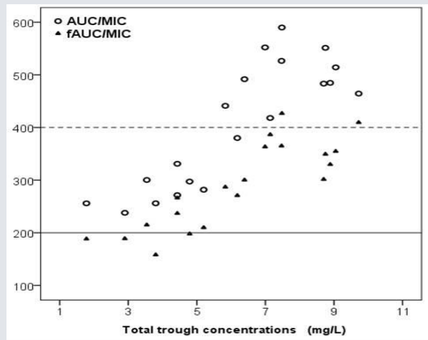

Figure 1: Correlation between total trough concentrations and (f)AUC/MIC for patients who received intermittent dosing. The dotted line indicates the target AUC/MIC of 400; the solid line indicates the target fAUC/MIC of 200; circles represent the calculated AUC/MIC; triangles represent the calculated fAUC/MIC. Spearman's Rank Correlation Coefficients for AUC/MIC R=0.85/p<0.01 and for fAUC/MIC R=0.82/p<0.01.

Variable	**Estimate**	**SE**	**p**
Total protein concentration	-0.50	0.095	<0.001
Intercept	100.91		
AIC	1259.39		
Albumin concentration	-0.68	0.16	<0.001
Intercept	95.10		
AIC	1264.54		

Table 2: Results of the linear mixed model analysis on free vancomycin fraction. Only the total protein and albumin can be withheld as covariates on the unbound vancomycin fraction. SE: Standard Error; AIC: Akaike's Information Criteria.

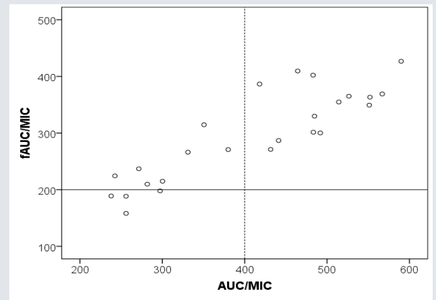

Figure 2: Correlation between AUC/MIC and fAUC/MIC. Vertical dotted line indicates target AUC/MIC of 400; horizontal solid line indicates target fAUC/MIC of 200; Spearman's Rank Correlation Coefficient R=0.88/p<0.01.

Variable	**Estimate**	**SE**	**p**
Total vancomycin concentration	0.71	0.0082	<0.001
Intercept	0.92		
AIC	794,13		
Total vancomycin concentration	0.71	0.0082	<0.001
Total protein concentration	-0.085	0.025	0.001
Intercept	5.38		
AIC	789.74		
Total vancomycin concentration	0.71	0.0081	<0.001
Albumin concentration	-0.11	0.041	0.008
Intercept	4.23		
AIC	791.62		

Table 3: Results of the linear mixed model analysis on free vancomycin concentration resulting in the following equation: free vancomycin concentration (mg/L) = 5.38 + 0.71 x total vancomycin concentration (mg/L) – 0.085 x total protein concentration (g/L). SE: Standard Error; AIC: Akaike's Information Criteria.

Discussion

The free vancomycin fraction in our patient population is noticeably higher than earlier reported in adults (approximately 50%) and exhibits high inter- and intravariability (Table 1). This may be explained by differences in protein concentrations, since we observed that the free fraction depended on total protein and albumin concentration, which were both decreased in our population (Table 2). Moreover, our data showed that target attainment rates varied widely upon the PK/PD target used (Table 1, Figure 1 and 2). As only the unbound concentration is pharmacologically active, these observations question the applicability of those targets, which were mainly derived from adult clinical studies in which total vancomycin concentrations were measured and a plasma protein binding of 50% was assumed. Since most institutions do not routinely measure unbound concentrations we provided a prediction tool that can be easily applied in paediatric clinical practice (Table 3). Further research is needed to validate PK/PD targets in patient populations with altered protein binding.

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