Serum and Cerebrospinal Fluid Concentrations of Vancomycin in Neurosurgical Critically Ill Patients with Proven or Suspected Central Nervous System Infections (P1204)

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Introductions

Combination therapy with meropenem and vancomycin is recommended for hospital-acquired central nervous system (CNS) infections [1]. The limited penetration of vancomycin into the cerebrospinal fluid (CSF) is well known. However, only limited data exist on the disposition of vancomycin in critically ill patients with CNS infections and non-inflamed meninges [2]. Vancomycin displays concentration-independent activity with the ratio of the area under the concentration time curve during a 24-hour time period (AUC0–24) to the minimal inhibitory concentration (MIC) as the primary predictive pharmacodynamic parameter for efficacy in serum [3].

The aim of this study was to describe concentrations of vancomycin in serum and CSF in critically ill patients with external CSF drainage and proven or suspected CNS infections.

Methods

Study design: This was an observational pharmacokinetic (PK) study in neurosurgical critically ill patients with proven or suspected CNS infection receiving vancomycin. Serial blood and CSF samples are taken and analysed by using an in vitro chemiluminescent micro particle immunoassay (ARCHITECT iVancomycin assay, Abbott; measuring range: 0,24 mg/l – 100,00 mg/l). Pharmacokinetic parameters are analyzed by a one compartment model.

Pharmacokinetic/Pharmacodynamic target: The primary pharmacokinetic/pharmacodynamic targets are the AUC divided by the minimum inhibitory concentration (MIC) value of 400 in serum and concentrations above the MIC of suspected pathogens throughout the entire dosing interval in CSF (100 % T>MIC). According to EUCAST 67 % of staphylococci display an MIC of 1 mg/l, 13 % display an MIC of ≤ 0,5 mg/l. Variables are described with median values [interquartile range].

Results

Ten patients (mean age 54, mean weight 73 kg) were enrolled. A total of 110 serum samples and 106 CSF samples were analyzed. In CSF, 31 % of the samples remained below the detection limit (presented as a maximum CSF concentration of 0,24 mg/l). Assuming an MIC of 0,5 mg/l all patients achieved an AUC/MIC value >400. Assuming an MIC of 1 mg/l 50 % of all sampling days achieved AUC/MIC > 400. In CSF, 56 % of all concentrations reached 1 mg/l and 32 % of all concentrations reached 2 mg/l.

Figure 1: Concentration of vancomycin in CSF (n= 10)

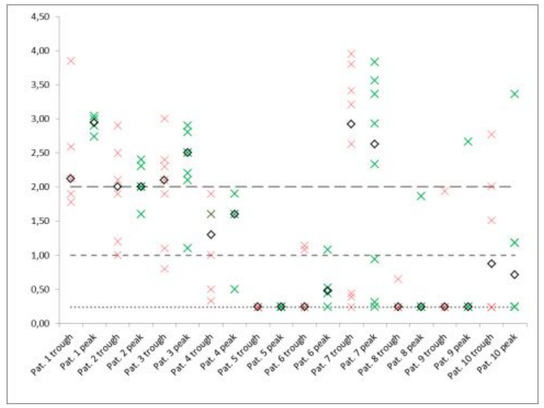

Figure 2: Concentrations of vancomycin in serum (n= 10)

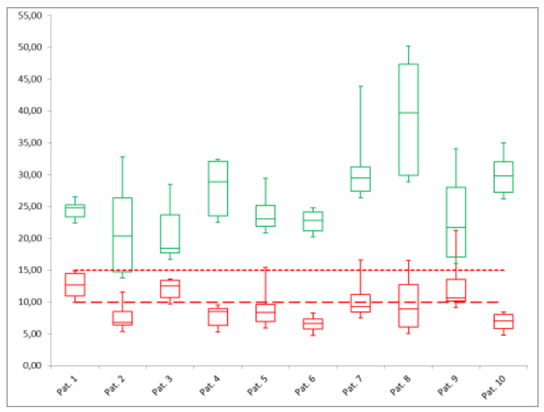

Figure 3: AUC of vancomycin in serum (n= 10)

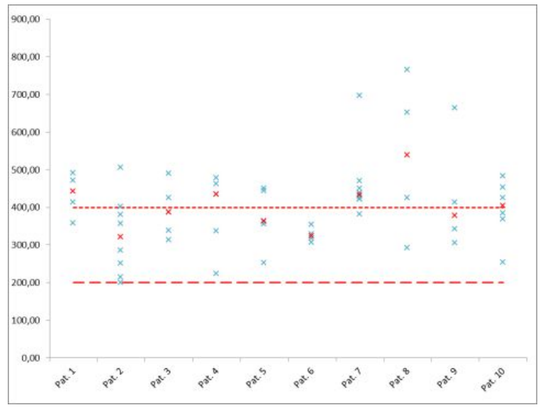

Table 1: Vancomycin median concentrations [mg/l] in serum and CSF (IQR = Interquartile Range)

Parameter	Pat. 1	Pat. 2	Pat. 3	Pat. 4	Pat. 5	Pat. 6	Pat. 7	Pat. 8	Pat. 9	Pat. 10
C max [mg/l] serum	24,78	20,35	18,40	28,90	23,07	22,83	29,52	39,69	21,75	29,82
IQR	1,88	11,60	6,00	8,60	3,33	3,01	3,85	17,47	10,94	4,83
C min [mg/l] serum	12,66	6,80	12,50	8,50	8,33	6,62	9,30	8,94	10,62	7,05
IQR	3,52	2,13	2,70	2,70	2,68	1,58	2,72	6,68	3,40	2,23
AUC [mg*l/h] serum	443,04	321,83	387,54	435,39	363,63	324,05	434,17	539,19	377,66	405,11
IQR	76,92	143,74	86,44	124,51	65,96	20,75	32,49	287,63	142,95	73,51
C max [mg/l] CSF	2,95	2,00	2,50	1,60	0,24	0,48	2,63	0,24	0,24	0,71
IQR	0,14	0,23	0,50	0,70	0,00	0,27	2,63	0,81	1,21	0,94
C min [mg/l] CSF	2,12	2,00	2,10	1,30	0,24	0,24	2,92	0,24	0,24	0,88
IQR	0,69	1,03	0,85	0,98	0,00	0,84	3,08	0,10	0,43	1,65

Table 2: Pharmacokinetic parameters

Parameter	Median	IQR	Range
C max [mg/l] serum	24,97	9,875	10,60 - 50,14
C min [mg/l] serum	8,64	4,36	4,46 - 21,23
AUC	394,77	112,95	200,04 - 765,30
$T_{1/2}$	5,09	3,79	3,33 - 17,49
Vd	0,63	0,225	0,31 - 2,10
C max [mg/l] CSF	1,60	2,26	0,24 - 3,83
C min [mg/l] CSF	1,12	1,87	0,24 - 3,95

Conclusions

Vancomycin demonstrated adequate CSF concentrations for high susceptible staphylpcocci/methicillinresistant staphylococcus aureus. (MHK < 1 mg/l). With the high inter-individual PK variability observed, therapeutic drug monitoring in CSF might be an option to optimize vancomycin dosing in critically ill patients with CNS infections. Higher serum level targets or switching to alternative antibiotics should be considered, if CSF concentrations are lacking.

References
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[3] Rybak MJ et al. Therapeutic monitoring of vancomycin in adults summary of consensus recommendations from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Pharmacotherapy. 2009;29(11):1275-9

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