UNIKLINIK KÖLN
Department of Pharmacology
University Hospital of Cologne

Plasma and cerebrospinal fluid population pharmacokinetics of vancomycin in patients with external ventricular drain

Zhendong Chen[1], Max Taubert[1], Chunli Chen[1,2], Charalambos Dokos[1], Uwe Fuhr[1], Thomas Weig[3], Michael Zoller[3], Suzette Heck[4], Konstantinos Dimitriadis[4,5], Nicole Terpolilli[5,6], Christina Kinast[3], Christina Scharf[3], Constantin Lier[7], Christoph Dorn[7], Uwe Liebchen[3]

[1]Department I of Pharmacology, University of Cologne, Cologne, Germany; [2]College of Veterinary Medicine, Northeast Agricultural University, Harbin, P.R. China; [3]Department of Anesthesiology, University Hospital, LMU Munich, Munich, Germany; [4]Department of Neurology, University Hospital, LMU Munich, Munich, Germany; [5]Institute for Stroke and Dementia Research, University Hospital, LMU Munich, Munich, Germany; [6]Department of Neurosurgery University Hospital, LMU Munich, Munich, Germany; [7]Institute of Pharmacy, Faculty of Chemistry and Pharmacy, University of Regensburg, Regensburg, Germany.

zhendong.chen@uk-koeln.de

Introduction

Background: Vancomycin is a standard therapy for central nervous system (CNS) infections, specifically nosocomial infections, caused by Gram-positive penicillin-resistant pathogens [1]. However, vancomycin cannot easily penetrate through the blood-brain barrier (BBB) into the cerebrospinal fluid (CSF) due to its pronounced hydrophilicity and large molecular weight [2]. Vancomycin CSF concentrations are highly variable also because the extent of vancomycin penetration depends much on the integrity of the BBB [3]. So far, only a few studies investigated CSF pharmacokinetics of vancomycin in neurological/neurosurgical, while available data in individual studies is sparse and validation of developed exposure predictors is limited.

Objective: (i) To investigate predictors for vancomycin penetration into CSF using a population pharmacokinetic (PopPK) approach based on vancomycin plasma and CSF data from patients who had an external ventricular drainage (EVD); (ii) to assess the feasibility of collecting CSF samples at the distal port of the EVD system for therapeutic drug monitoring (TDM); (iii) to examine the benefits of different infusion modes and dosages through model-based simulations.

Demographics and covariates

Characteristic	Patients with primary CNS infection	Patients without primary CNS infection
Demographics		
Male	7	4
Female	2	1
Age (years)	59.7 (11.8)	37.0 (10.2)
Body weight (kg)	84.2 (25.0)	88.6 (16.6)
Height (cm)	174 (6)	179 (9)
Covariates in plasma		
CrCL (mL/min)	142 (57)	194 (41)
Creatinine (mg/dL)	0.671 (0.138)	0.693 (0.287)
Covariates in CSF		
Protein (mg/dL)*	108 (53)	27.4 (29.0)
Glucose (mg/dL)*	51.4 (21.7)	80.4 (13.5)
Lactate (mmol/L)*	4.63 (0.98)	1.78 (0.43)
S100 protein (µg/L)	3.88 (2.13)	30.0 (0.0)
Neuron-specific Enolase (µg/L)	15.6 (4.9)	326 (199)
Ferritin (µg/L)	501 (92)	264 (277)
Erythrocytes (10^3 µg/L)	137 (127)	4.85 (5.37)
Cell count (cells/µL)	292 (128)	170 (316)
Interleukin 6 (10^3 ng/L)	157 (278)	5.65 (8.66)

☐ Patients were classified according to whether the primary infection was a CNS infection or not and table are shown as mean (SD).
☐ Blood and CSF samples from the proximal port (CSF_P) or distal port (CSF_D) of the EVD system were collected for measurements of vancomycin concentrations and clinical parameters [4].
☐ Vancomycin was administered by intermittent infusion and/or continuous infusion (with or without an initial loading dose).

Model development

☐ Software: NONMEM (version 7.4) and Perl-speaks-NONMEM;
☐ Statistical criteria: ΔOFV>3.84 ($P < 0.05$) for inclusion of one parameter between nested models; AIC were compared between non-nested models;
☐ Plasma base model was firstly developed using plasma data only;
☐ CSF model was directly linked to the central compartment;
☐ Two empirical CSF base models were compared and assessed separately [5,6];
☐ Bulk flow model was chosen and Q_{bulk} was fixed at 0.025L/h;
☐ Power model was used for continuous covariates and conditional effect was used for categorical covariates.

Transit compartment model   *Bulk flow model*
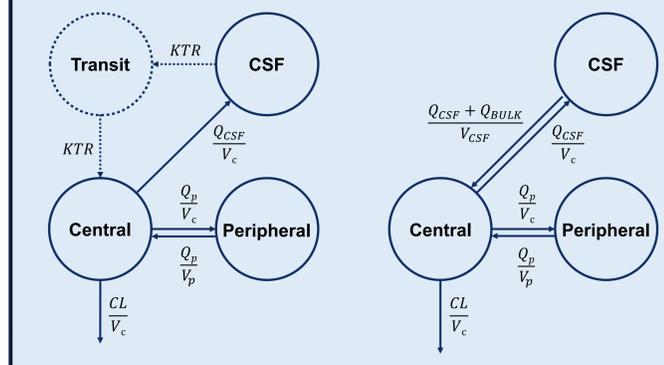
Figure 1 Scheme of the transit compartment model (left, $V_{CSF} = 0.002$ L/kg × weight) and the bulk flow model (right, $Q_{BULK} = 0.025$ L/h, preferred and used for further evaluations) for CSF compartment.

Parameter estimates

Parameters	Final model		927 successful bootstrap runs	
	Estimate	RSE (%)	Median	95% confidence interval
CL (L/h)	4.53	7.5	4.52	3.74 – 5.29
V_c (L)	24.0	8.6	23.3	16.6 – 27.0
Q_p (L/h)	5.69	12.2	5.70	4.43 – 8.64
V_p (L)	38.7	16.5	39.7	27.9 – 59.1
Q_{CSF}_1 (L/h)	0.00322	5.6	0.00331	0.00263 – 0.00390
Q_{CSF}_2 (L/h)	0.00135	29.9	0.00129	0.000938 – 0.00383
V_{CSF} (L)	0.445	14.7	0.465	0.244 – 0.883
Covariates				
CrCL on CL	0.453	27.6	0.452	0.150 – 0.830
Age on Q_p	2.69	24.4	2.84	1.37 – 4.74
Protein (CSF) on Q_{CSF}_1	1.09	6.0	1.10	0.808 – 1.67
Protein (CSF) on Q_{CSF}_2	0.575	21.9	0.575	0.203 – 1.03
Inter-individual variability				
CL (%)	29.5 (0.1%)	18.7	27.9	15.9 – 38.1
V_p (%)	54.3 (20.6%)	25.1	54.9	21.4 – 93.7
Q_{CSF} (%)	19.8 (17.7%)	20.8	13.6	4.7 – 25.1
V_{CSF} (%)	94.2 (10.1%)	20.8	105.0	36.1– 175.7
Residual variability				
Proportional error (Plasma, %)	15.9 (5.3)	15.5	15.4	10.7 – 20.4
Proportional error (CSF, %)	27.5 (3.8)	5.6	26.5	17.3 – 34.7

CL, clearance; V_c, the central compartment volume; Q_p, inter-compartment clearance of central and peripheral compartments; V_p, the peripheral compartment volume; CrCL, creatinine clearance; Q_{CSF}_1, inter-compartment clearance between plasma and CSF compartment in patients with primary CNS infection; Q_{CSF}_2, inter-compartment clearance between plasma and CSF compartment in patients without primary CNS infection; V_{CSF}, the CSF compartment volume. RES: relative standard error.

Model diagnosis
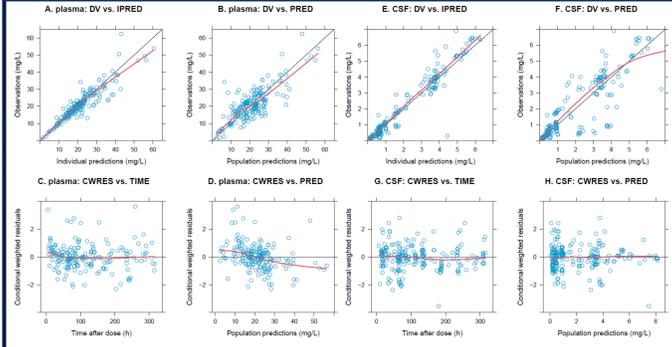
Figure 2 Combined goodness-of-fit plots of the final model for vancomycin plasma (A – D) and CSF (E – H) concentrations.
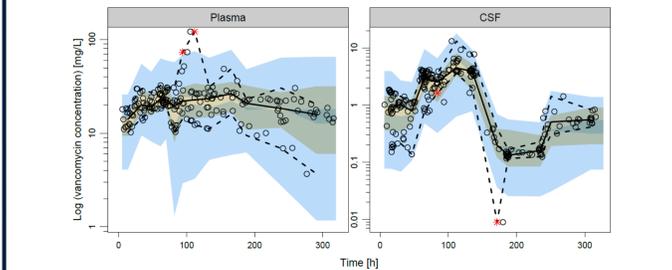
Figure 3 Confidence interval prediction-corrected visual predictive check ($n = 1000$) for the final model for plasma and CSF observations.

Covariate vs. PK/PD target

Figure 4 Simulated plasma AUC_{24} depending on estimated CrCL in patients with primary central nervous system infection after different dosing regimens ($n = 3000$) in first 24 hours of vancomycin treatment. The solid line represents the median while dashed lines show the 5th and 95th percentile of predicted AUC_{24}.
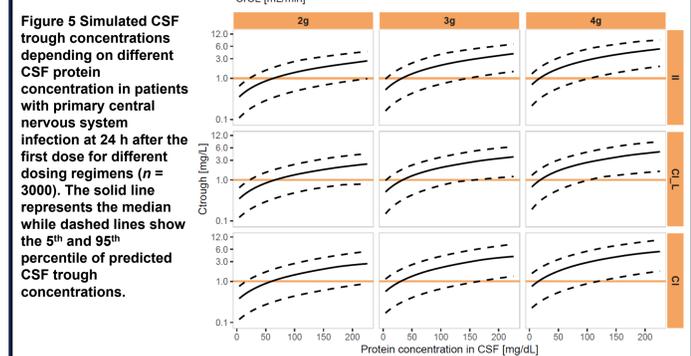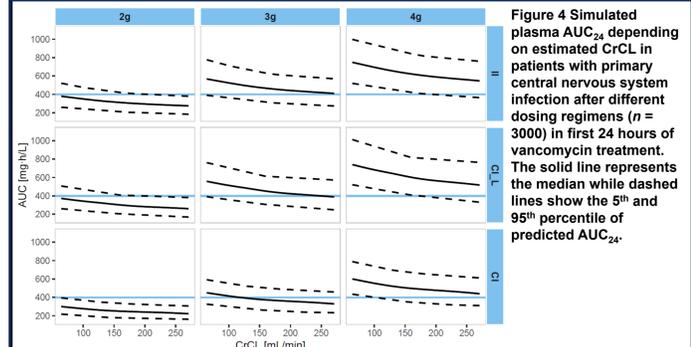
Figure 5 Simulated CSF trough concentrations depending on different CSF protein concentration in patients with primary central nervous system infection at 24 h after the first dose for different dosing regimens ($n = 3000$). The solid line represents the median while dashed lines show the 5th and 95th percentile of predicted CSF trough concentrations.

Plasma AUC_{24} or CSF C_{trough}

Probability of target attainment (PTA; plasma AUC_{24} or CSF C_{trough}) in simulated patients with primary central nervous system infection after different dose regimens of vancomycin on day 1 and at steady state (in parentheses).

PK/PD target	II (q12h)			CI_L			CI		
	2 g/24 h	3 g/24 h	4 g/24 h	2 g/24 h	3 g/24 h	4 g/24 h	2 g/24 h	3 g/24 h	4 g/24 h
Plasma AUC_{24} (mg·h/L)									
> 200	96.0 (98.8)	99.9 (99.9)	100 (100)	94.5 (98.7)	99.9 (100)	100 (100)	84.1 (99.0)	99.7 (100)	100 (100)
> 400	12.0 (56.9)	72.4 (91.3)	96.0 (98.8)	11.3 (59.6)	67.1 (92.1)	94.5 (98.7)	0.7 (61.7)	36.1 (92.7)	84.1 (99.0)
> 600	0.1 (15.5)	18.9 (85.6)	54.0 (86.6)	0 (17.0)	15.4 (59.6)	48.2 (85.8)	0 (17.7)	3.3 (61.3)	28.2 (87.3)
CSF C_{trough} (mg/L)									
> 0.5	87.5 (98.4)	94.0 (99.7)	96.7 (100)	87.1 (99.0)	94.1 (99.9)	96.8 (100)	86.4 (99.3)	93.4 (99.9)	96.6 (100)
> 1.0	64.2 (89.2)	80.7 (96.0)	87.5 (98.4)	62.5 (92.0)	78.7 (99.1)	87.1 (92.4)	64.3 (97.8)	78.7 (99.3)	86.4 (99.3)
> 2.0	27.6 (63.7)	49.9 (81.4)	64.2 (89.2)	23.5 (70.3)	47.6 (85.7)	62.5 (92.0)	29.7 (70.1)	51.0 (85.8)	64.3 (92.4)

Plasma AUC_{24}
➢ Plasma AUC_{24} of CI is lower than that of II and CI_L on day 1, but there were no difference in PTA between 3 infusion modes at steady state;
➢ Daily dose of 2 g is sufficient whether by II or CI_L to achieve AUC_{24} > 200 mg·h/L in >90% simulated patients;
➢ Patients with CrCL < 150 mL/min need a daily dose of 3 g whereas patients with CrCL > 150 mL/min may require a daily dose of 4 g to achieve AUC_{24} > 400 mg·h/L;
➢ Daily dose of 4 g would cause at least 28.2% of patients to face a potential plasma AUC_{24} above 600 mg·h/L, which may lead to a higher risk of acute kidney injury.

CSF C_{trough}
➢ The three infusion modes with same daily dose resulted in similar levels of C_{trough} in CSF on day 1 and at steady state.

Simulations: 3 infusion modes
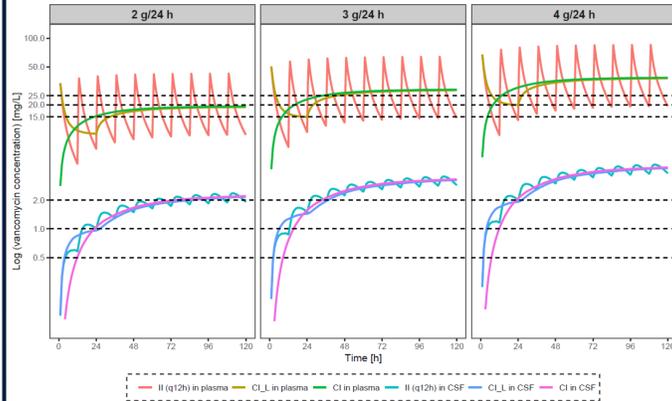
Figure 6 Median concentration vs. time curves simulated in plasma and CSF after different dosing regimens of vancomycin over 5 days in patients with CNS infection. II: intermittent infusion; CI_L: continuous infusion with loading dose same as the first dose of q12h; CI_L: continuous infusion with loading dose same as the first dose of q12h; CI: continuous infusion without loading dose.

➢ II and CI_L allowed to reach presumed same target concentrations in CSF faster compared with CI;
➢ CI could keep plasma concentrations relatively low during the therapy;
➢ If the target Ctrough in CSF is 1 mg/L, adjustment of doses according to CSF protein concentrations of ≥150, <150 & ≥100, and <100 mg/dL would result in daily doses of 2, 3, and 4 g vancomycin which were then linked to a PTA of 90.4%, 90.8%, and 69.6%, respectively, in simulated patients;
➢ Excessive systemic exposure would also prohibit using even higher vancomycin doses in order to achieve higher CSF PTA in patient with low CSF protein concentration.

Conclusions

✓ A PopPK model for vancomycin was successfully established using the data from patients with EVD;
✓ Three substances quantified in CSF were identified as predictors associated with vancomycin CSF concentrations, while the relationship was closest with CSF protein;
✓ The model fully supported feasibility of collecting CSF sample at the distal port of the EVD system for TDM;
✓ Recommendations on dosing regimen for patients with CNS infection were provided according to different CSF protein levels;
✓ Beyond adjusting doses according to renal function, starting treatment with a loading dose in patients with primary CSF infection is recommended.

References

1. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2009; 66:82-98.
2. Lutsar I, McCracken GH Jr, Friedland IR. Antibiotic pharmacodynamics in cerebrospinal fluid. Clin Infect Dis. 1998; 27(5):1117-27, quiz 1128-9.
3. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006; 42 Suppl 1:S35-9.
4. Kinast CB, Paal M, Liebchen U. Comparison of Cerebrospinal Fluid Collection Through the Proximal and Distal Port Below the Overflow System from an External Ventricular Drain. Neurocrit Care. 2022; 37:775-778.
5. Jalusic KO, Hempel G, Arnemann PH, et al. Population pharmacokinetics of vancomycin in patients with external ventricular drain-associated ventriculitis. Br J Clin Pharmacol. 2021; 87:2502-2510.
6. Büsker S, Jäger W, Poschner S, et al. Pharmacokinetics of metronomic temozolomide in cerebrospinal fluid of children with malignant central nervous system tumors. Cancer Chemother Pharmacol. 2022; 89:617-627.