Cerebrospinal fluid penetration of vancomycin in critical care patients with proven or suspected ventriculitis: a prospective observational study

Running Titel: Cerbrospinal fluid penetration of vancomycin

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1. Synopsis

Background: Vancomycin is recommended for ventriculitis. However, penetration into the CNS is relatively poor.

Objectives: To investigate the population pharmacokinetics of vancomycin serum and CSF in critical care patients with proven or suspected CNS infections from neurosurgical procedures.

Patients and methods: This was an observational pharmacokinetic study in critical care patients with proven or suspected CNS infections receiving intravenous vancomycin. Multiple blood and intraventricular CSF samples were collected. Population pharmacokinetic analysis and simulation were undertaken with ADAPT5 and Pmetrics.

Results: 187 blood and CSF samples were collected from 21 patients. The median (range) C_{max} and C_{min} concentrations in serum were 25.67 (10.60-50.78) and 9.60 (4.46-23.56) mg/L, respectively, with a median daily dose of 2500 (500-4000) mg. The corresponding median concentrations in CSF was 0.65 (<0.24-3.83) mg/L and 0.58 (<0.24-3.95) mg/L, respectively. The median AUC_{0-24} in serum and CSF was 455.09 mg*h/L and 14.10 mg*h/L, respectively. A three-compartment linear population pharmacokinetic model best fitted the observed data. Vancomycin demonstrated poor penetration into CSF, with a median CSF/serum ratio of 3% and high inter-subject pharmacokinetic variability of its penetration.

Conclusion: Therapeutic drug monitoring (TDM) in both serum and CSF and higher daily doses may be an option to ensure adequate trough levels and to optimize patient therapy. Novel dosing strategies designed to reduce renal toxicity, such as administration by continuous infusion, should be investigated in further clinical studies to avoid antibiotic underexposure in CSF.

2. Introduction

Gram-positive cocci, especially *Staphylococcus* spp., are the leading cause of surgical site infections resulting from neurosurgical procedures.[1] Despite the development of novel antibiotics active against Gram-positive pathogens, vancomycin generally remains the standard of care, particularly of methicillin resistant MRSA and methicillin resistant *Staphylococcus epidermidis* (MRSE).[2] Furthermore, vancomycin is used in combination with meropenem as empiric antibiotic therapy in critical care patients with infections of the CNS such as meningitis or ventriculitis.[1] However, in the absence of meningeal inflammation the penetration into CSF of vancomycin is hampered by its large molecular weight and hydrophilicity.[3, 4] Recent data suggest there is highly variable penetration of vancomycin into the CSF.[5] Relatively little is known about the pharmacokinetics (PK) of vancomycin in the CSF of patients with ventriculitis.[5, 6]

A serum AUC/MIC value of 400 in serum is often used as a pharmacodynamic target.[2] There is less clarity about the relevant drug exposure at the target site of infection (e.g. the CSF for critical care patients with proven or suspected CNS infections) and the regimens required to achieve these targets. Conventionally used regimens of 500 mg every 6 h (q6h) or 1 g every 12 h (q12h) have little evidence supporting their efficacy in specific populations particularly critically ill patients.[7] Guidelines recommend 30-60 mg/kg/day vancomycin for meningitis and ventriculitis to ensure sufficient CSF concentrations.[1, 2] Due to very few studies in meningitis patients an alternative agent should be considered, if vancomycin MIC is ≥1 mg/L.[1] However, drug as well as disease factors, such as the presence of meningeal inflammation and the integrity of the blood-liquor barrier, are important to consider when devising dosing strategies.[3, 4, 6] The meninges in ventriculitis are typically normal or only minimally inflamed.[3, 4, 6] Therefore, penetration into the CNS in patients with ventriculitis should not be extrapolated from other patient populations.[3, 4, 6]

The purpose of this study was to investigate the population pharmacokinetics of vancomycin in serum and CSF in critical care patients with external ventricular drains (EVD) and proven or

suspected ventriculitis. Such an analysis is fundamental to characterize the inter-individual variability of vancomycin concentrations in CSF and to further investigate optimal vancomycin regimens for patients with ventriculitis.

3. Patients and methods

3.1. Study design and population

This prospective observational PK study was conducted at the intensive care unit of Munich Ludwig-Maximilians-University (LMU) Hospital, Germany between April 2014 and January 2016. Patients older than 18 years of age who required an EVD and in whom a proven or suspected EVD-associated ventriculitis developed were enrolled in the study. The diagnosis of ventriculitis was defined as a positive CSF culture combined with clinical signs of infection.[8] Suspected ventriculitis was defined by abnormal CSF parameters, such as low CSF glucose levels (<50% of serum glucose), high CSF protein (>50 mg/dL) or CSF pleocytosis, combined with clinical signs of infection in the absence of a positive CSF culture.[8] Patients were excluded if they were under 18 years of age or death within 72 h was expected.

3.2. Ethics

The trial was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the university ethics committee (registration number 111-14). Written informed consent was obtained from all patients or a legally authorized representative before enrolment.

3.3. Study procedures

All included patients received vancomycin (Vancomycin CP®, Hikma Pharma, Germany) as a prolonged infusion over 4 h, targeting trough concentrations of 10-15 mg/L in serum. Serial blood and CSF sampling occurred for initial dose and steady state. Blood samples (4 mL) were collected using the indwelling arterial catheter just before the start of the infusion (trough concentration; C_{min}) and after the end of the infusion (peak concentration; C_{max}). CSF samples

(1 mL) were collected using the indwelling EVD nearest to the site of insertion (3 mL volume to sampling location) simultaneously with each blood sample just before the start of the infusion (cerebrospinal fluid concentration at serum trough concentration [C_{trough}]) and after the end of the infusion (cerebrospinal fluid concentration 4 h after serum trough concentration [$C_{after\ 4h}$]). Samples were centrifuged for 5 minutes at 4000 rpm and stored at −80 °C within 45 minutes after sample collection for a maximum of 4 weeks until the measurement of drug. Serum and CSF concentrations of vancomycin were analysed using an *in vitro* chemiluminescent micro particle immunoassay (ARCHITECT *i*Vancomycin assay, Abbott; measuring range: 0.24 mg/L-100.00 mg/L). For CSF concentrations of vancomycin, spiked CSF samples were carried out on a regular basis in addition to the routine validation process. Only vancomycin total concentration (bound plus unbound) was measured.

Additional data were obtained from the medical record including weight, height, serum creatinine, bilirubin, serum C-reactive protein (CRP), serum interleukin-6 (IL-6), serum procalcitonin (PCT), serum leucocytes, CSF cells, CSF erythrocytes, CSF IL-6, CSF glucose, CSF protein, CSF drain in 24 h, Simplified Acute Physiology II Score (SAPS II), SOFA Score, Glasgow Coma Score (GCS), and dexamethasone therapy.

3.4. Population pharmacokinetic analysis

A three-compartment model with zero order infusion for vancomycin was fitted to the study data.[9] The structural model took the form:

(1) $dX_C/dt = R(t) - (SCL/V_c + k_{cp} + k_{cb}) \times X_C + k_{pc} \times X_P + k_{bc} \times X_{CSF}$

(2) $dX_P/dt = k_{cp} \times X_C - k_{pc} \times X_P$

(3) $dX_{CSF}/dt = k_{cb} \times X_C - k_{bc} \times X_{CSF}$

The three equations above describe the rate of change of vancomycin (mg) in the central (1), peripheral (2) and CSF (3) compartments, respectively. The equation elements are defined in figure 1 legend. Equation (1) describes the rate of change of the amount of vancomycin (in milligrams) in the central compartment (X_C). Equation (2) describes the rate of change of the

amount of vancomycin (in milligrams) in the peripheral compartment (X_P). Equation (3) describes the rate of change of the amount of vancomycin (in milligrams) in the CSF (X_{CSF}). A schematic representation of the structural model is shown in Figure 1.

We used the Pmetrics package v. 1.5.0.[10] to model the concentration-time data for vancomycin, simulate from the model, generate plots and perform standard data summaries and statistical tests. The observed data were weighted by the inverse of individual error coefficients that were obtained using the maximum likelihood estimator in ADAPT 5. Additional process noise such as errors in sampling time or dosing was modelled using gamma as a multiplicative error term in Pmetrics.

3.5. Population pharmacokinetic model diagnostics

Acceptance of the final model was evaluated by the log-likelihood, the coefficient of determination (r^2) of the linear regression and visual inspection of diagnostic scatterplots, where model predictions were generated either by the median population parameter values or by the medians of each subject's individual Bayesian posterior parameter value distributions.

3.6. Population pharmacokinetic covariate screening

The impact of weight, height, CrCL, bilirubin, serum CRP, serum IL-6, serum PCT, serum leucocytes, CSF cells, CSF erythrocytes, CSF IL-6, CSF glucose, CSF protein, CSF drain in 24 h, SAPS II, SOFA Score, GCS and dexamethasone therapy as covariates were initially assessed by visual inspection. For that reason, graphical representation in Pmetrics of each covariate versus population parameter was performed to evaluate for inclusion in the final model.

3.7. Other pharmacokinetic calculations

C_{max}, C_{min}, $C_{after\ 4h}$, and C_{trough} are the observed values. AUC in serum and CSF was calculated using the Bayesian estimates from each patient using the trapezoidal rule that is implemented

within Pmetrics. We divided each subject's cumulative AUC by the total time in hours and multiplied the result by 24 to estimate the daily average AUC ($AUC_{0–24}$). The correlation between these values was assessed using Pearson's test. Penetration of vancomycin into CSF was described using the CSF/serum ratio, which was calculated by dividing the cumulative AUC in CSF by the cumulative AUC in serum. Half-life was calculated using transfer rate constants. Creatinine clearance (CrCL) was calculated using the Cockcroft-Gault equation.[11] All calculations were performed using IBM SPSS Statistics version 23.0 software (IBM, Armonk, NY, USA).

3.8. Assessment of vancomycin concentration in CSF

We performed simulation of 3000 patients using Pmetrics to compare different dosing regimens in this study population (1000 mg every 12 h, 2000 mg every 12 h with each administered as a 4 h infusion. Additionally, the outcome of 4000 mg, and 6000 mg administered as a continuous infusion was examined). A PTA in CSF was analysed using Pmetrics targeting vancomycin concentrations of 0.25 mg/L, 0.5 mg/L, 1 mg/L, and 2 mg/L.

4. Results

The study included 196 blood samples and 186 CSF samples from 21 patients. Detailed demographic characteristics are presented in Table 1. One CSF sample was excluded from the study because of concentration 3 times the standard deviation (n=1). Serum samples were excluded because of uncertain sample collection time (n=2).

The study population was relatively young (median age 52 years, range 46–80 years) and had well-preserved renal function on the day of inclusion (median CrCL 120.1 ml/min, range 52.3-217.6 ml/min). The median (range) SAPS II score was 47 (13–62). All patients received meropenem therapy in addition to vancomycin. Seven patients (33.3%) received concomitant fosfomycin for 7 days, although one (4.8%) of them also received rifampicin, which then was replaced by fosfomycin. Patient 1 additionally received dexamethasone during the first 2 days, and patient 14 additionally received dexamethasone during the first 5 days.

The most frequent neurological disease was subarachnoid haemorrhage, which was diagnosed in 17 (81.0%) patients. In the remaining four patients, an EVD was placed for intracranial bleeding (4.8%), tumour (9.5%) or traumatic brain injury (4.8%). A total of 20 patients (95.2%) were CSF culture-negative, and one patient (4.8%) had a positive culture for *Pseudomonas aeruginosa*. In serum, median C_{max} (range) was 25.67 (10.60-50.78) mg/L and median (range) C_{min} was 9.60 (4.46-23.56) mg/L. In CSF, median C_{max} (range) was 0.65 (<0.24-3.83) mg/L and median C_{min} 0.59 (<0.24-3.95) mg/L. In total, 64 CSF samples were below the detection limit. Median daily dose of vancomycin was 2500 (500-4000) mg administered in two divided doses. Individual observed vancomycin concentrations and doses are shown in Table S1, available as supplementary data at *JAC* Online. CrCL on sample days ranged from 52.3 to 122.5 mL/min (median CrCL 122.5 mL/min). The median AUC_{0-24} in CSF was 14.10 mg*h/L and in serum 455.09 mg*h/L. The median values for the AUC_{0-24} in CSF and serum ranged from 2.64 to 81.30 mg*h/L and 277.35 to 521.02 mg*h/L, respectively. The median CSF/serum ratio (range) was 0.03 (0.01-0.18). There was no statistically significant correlation between the AUC in serum and CSF (r=-0.112, p=0.629). Individual AUC_{0-24} and penetration results are shown in Table S2, available as supplementary data at *JAC* Online.

4.1. Pharmacokinetic model building

The fit of the mathematical model to the observed data was acceptable according to visual inspection of the observed-versus-predicted plots and r^2 of the observed-versus-predicted values (r^2 = 0.930 in serum, r^2 = 0.579 in CSF) (Figure S1, available as supplementary data at *JAC* Online). Individual PK results in serum and CSF obtained by Pmetrics for the PK model are shown in Table S2. The mean, median, and SD for the population parameters identified by Pmetrics for the PK model are shown in Table 2. Population parameter value covariance matrix are shown in Table S3, available as supplementary data at *JAC* Online. Values of these pharmacokinetic parameters in the population were estimated by using all data, replacing data below the quantification limit with the value QL/2, where QL is the quantification limit.[12] No covariate relationships could be supported for any of the model parameters.

4.2. Assessment of vancomycin concentration in CSF

Simulated vancomycin concentration–time profiles in serum and CSF of each regimen are shown in Figure 2. The simulated AUC in steady-state of vancomycin 1000 mg every 12 h is shown in Figure 3. Vancomycin concentrations in CSF greater than or equal to 0.25 mg/L, 0.5 mg/L, 1 mg/L, and 2 mg/L were exceeded in 99.8%, 96.0%, 61.4%, and 0.1 % of simulated patients, respectively for a regimen of 2000 mg every 12 h. Similarly, these thresholds were exceeded in 87.2%, 57.8%, 5.6%, and 0% of simulated patients receiving 1000 mg every 12 h. With continuous infusion vancomycin concentrations in CSF greater than or equal to 0.25 mg/L, 0.5 mg/, 1 mg/L, and 2 mg/L were exceeded in 100.0%, 100.0%, 96.8%, and 25.6% of patients receiving a daily dose of 6000 mg, and in 100.0%, 97.4%, 67.4%, and 0.3% receiving a daily dose of 4000 mg.

5. Discussion

To our knowledge, this is the first population PK study of vancomycin concentrations in serum and CSF in critical care patients with proven or suspected ventriculitis. We found that penetration of vancomycin into CSF is poor, with a median penetration ratio of only 3% and a large intersubject variability in CSF vancomycin concentration as well as resultant CSF/serum ratios. However, PK variability in CSF was not explained by any covariates. Our study suggests the additional need for therapeutic drug monitoring of vancomycin in CSF if vancomycin MIC is ≥1 mg/L to avoid treatment failures due to underexposure in CSF and to identify patients for a change of therapy.

It is generally accepted, that the drug penetration into CSF is indicative of the transport across the choroid plexus at the blood–CSF barrier.[13] Therefore, a separate CSF compartment was considered in our model and linked to the central compartment by a first-order process. Our PK model suggest that vancomycin penetration (median $t_{1/2cb}$ 9 h) into CSF is slower than CSF clearance (median $t_{1/2bc}$ 8 h) (Table S2). This is consistent with other studies in ventriculitis patients[14] as well as in non-inflamed meninges.[15] CSF drain volume from the EVD can be high in patients with hydrocephalus after placing the EVD. Therefore, loss through an EVD could

be an additional route of drug elimination from CSF.[16] However, a CSF drain over the course of treatment was not found to influence the pharmacokinetics of vancomycin. The high apparent volume of CSF reflects the relatively low CSF concentrations compared with serum. V_{CSF} is not a physiological CSF volume; it is merely a scalar that explains the concentration observed in the CSF. Previous studies identified CSF albumin level as a determinant of CSF vancomycin concentration.[16-18] However, albumin level as a predictor of the blood brain barrier is not validated in patients with external drain.[19] This is because an increased CSF albumin is influenced by blood in the CSF through subarachnoid bleeding or intracerebral bleeding. Furthermore, CSF albumin may vary with time and patients in previous studies were included after neurosurgery for only 72 h.[16-18] Since the majority of EVD-related infections occurs within the first 5 to 14 days after insertion, CSF albumin level as a surrogate guide to CSF vancomycin concentration should not be extrapolated to ventriculitis patients.[20, 21] In our study, all patients were at least five days post neurosurgery.

Vancomycin does not show universally low penetration into CSF. While penetration in inflamed meninges is reportedly as high as 81%, penetration into CSF in normal or mildly infected meninges are conflicting varying from 0 – 36%.[5] Other studies suggest that neurosurgical procedures may damage the blood-brain-barrier and facilitate penetration of vancomycin into CSF.[16, 18] Although, many studies have estimated CSF penetration using a single point estimates of serum and CSF vancomycin concentrations. Vancomycin CSF-to-serum ratios in six patients with ventriculitis ranged from 5 to 17%, with patients achieving CSF concentrations of 1.1–6 mg/L.[5] This variability is consistent with the PK variability in our study population with penetration ranging from 1 to 18%. No covariate predicted vancomycin CSF penetration, as reported by Beach and colleagues.[5] Furthermore, there was no statistically significant correlation between plasma AUC and CSF AUC, which poses challenges for the use of serum TDM to ensure therapeutic concentrations in CSF. However, 34% of our CSF samples showed very low vancomycin concentrations. Patients with ventriculitis may benefit from continuous infusion to ensure higher CSF concentrations of vancomycin.[15, 22] Continuous infusion may also simplify therapeutic drug monitoring (TDM) in daily routine because concentration

measurement is time-independent and facilitates calculation of the AUC. As reported by Neely and colleagues, more than approximately 50% of the interindividual variability in the AUC are not explained by trough concentration.[23] Further clinical studies are warranted to investigate the pharmacokinetics, safety and efficacy of vancomycin infusions for the treatment of ventriculitis.

From a PD point of view, MRSA and MRSE are the most challenging pathogens in nosocomial CNS infection.[1] It is unclear which PK-PD target should be used to optimise the outcome for infections within the CNS.[6, 24] Data from an experimental pneumococcal meningitis model suggest peak concentration of vancomycin 4 times the MBC for a maximal bacterial killing rate in CSF.[25] An AUC/MIC value of 400 has been established as the PK - PD target in serum based on in-vitro and animal data.[2] In CSF of our patients, an AUC/MIC target of 400 is hardly exceeded. More work is required to better understand PD targets at the site of infection for patients with ventriculitis. In our study, 61.4% of the simulated patients with 2000 mg every 12 h as a prolonged infusion exceeded CSF trough concentrations of 1 mg/L assuming all drug in the CSF is unbound, whereas 96.0% exceeded 0.5 mg/L.

Patients in our study were generally young without any measured renal dysfunction on day of inclusion (median CrCL 122 mL/min, Table 1) in contrast to the renal function in other studies (mean CrCL 90 mL/min [26], 56 mL/min and 78 mL/min [23]). In concordance vancomycin clearance in serum (6 L/h) was higher comparing to other PK studies in critically ill patients (4.6 L/h [26], 3.0 L/h [23]). In severe infections and/or deep infections trough concentrations in serum of 15-20 mg/L (AUC of 600-800 mg/L*h) are recommended.[1, 2] Young patients with augmented renal clearance presented in this study (8 of 21 patients with CLCr ≥ 130 mL/min, Table S1) are at high risk of insufficient concentrations of vancomycin with conventional dosing regimens. Therefore, in critical care patients with CNS infections caused by MRSA or MRSE with an MIC ≥ 1 mg/L, the standard dosing regimen of vancomycin 2000 every 12 h as a prolonged infusion is unlikely to ensure adequate CSF concentrations. However, TDM in CSF may identify patients with sufficient vancomycin concentrations in CSF. In those displaying

ARC, increased frequency of dosing or continuous infusion with serum AUC of 600-720 mg/L*h may be more appropriate.[27] In addition, continuous infusion may reduce renal toxicity especially with high doses.[28] Alternatives like linezolid, daptomycin or sulfmethoxazol-trimethoprim should be considered in patients with high serum concentrations (AUC up to 800 mg/L*h) and low CSF concentrations (<1 mg/L).[1]

There are several limitations of our study. First, the study was relatively small, which may have hampered robust estimates of the extent of PK variability and the identification of covariates that may have explained some of the observed variance. CrCL was estimated, because the measurement is not routinely performed in routine clinical care. Secondly, pharmacokinetic data were not adjusted for protein binding, because we measured the total concentration in serum and CSF. Due to negligible protein levels in CSF compared to serum and that protein binding of vancomycin in not high, CSF concentrations might be free concentrations for vancomycin. However, protein binding of vancomycin in the CSF is currently unknown. Third, the ethical approval allowed two samples per day and of the 186 samples, 64 (34%) were reported below the limit of quantification which might have an impact on the final parameter estimates from the population PK model.

In conclusion, this is the largest PK study of critical care patients with proven or suspected ventriculitis. Population pharmacokinetic modeling approach is a useful tool to predict drug exposure under different dosage regimens. We found, that vancomycin showed low penetration into CSF. However, because of inter-subject variability of vancomycin TDM in both serum and CSF and higher daily doses may be an option to ensure adequate trough levels at the target site of infection and to identify patients for a change of therapy. Novel dosing strategies of vancomycin should be investigated in further clinical studies in ventriculitis therapy such as administration by continuous infusion in order to reduce renal toxicity and to avoid antibiotic underexposure in the context of augmented elimination or impaired target site penetration.

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Transparency declarations:

The authors declare that they have no competing interests.

Authors' contributions:

UB participated in the design of the study, measured vancomycin concentrations by immunoassay, was responsible for acquisition of data, performed the pharmacokinetic analysis and drafted the manuscript. VH conceived of the study, participated in its design and coordination, and was responsible for acquisition of data. ORF participated in the design of the study, including interpretation of results, and measured vancomycin concentrations by immunoassay. CVK participated in the design of the study, including interpretation of results, and was responsible for acquisition of data. ACR measured vancomycin concentrations by immunoassay. WH performed the pharmacokinetic analysis and helped to draft the manuscript. NT made substantial contributions to the conception and design of the study and also interpreted the results. JB made substantial contributions to the conception and design of the study and also interpreted the results. All authors critically revised the manuscript for important intellectual content, and all authors read and approved the final manuscript.

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Age (years), median (range)	52 (46-80)
Weight (kg), median (range)	76 (55-105)
Body mass index, median (range)	25.95 (20-33)
Sex, %male/%female	52,4%/47,6%
CrCL on day of inclusion (mL/min), median (range)	120.1 (52.3-217.6)
CRP in serum on day of inclusion (mg/dL), median (range)	3.1 (0.4-36.7)
Interleukin 6 in serum on day of inclusion (pg/mL), median (range)	13.7 (2.4-274.0)
CSF drain in 24 h on day of inclusion (mL), median (range)	183 (21-360)
Interleukin 6 in CSF on day of inclusion (pg/mL), median (range)	3398 (140-24522)
Cells in CSF on day of inclusion (/uL), median (range)	503 (4-2894)
Protein in CSF on day of inclusion (mg/dL), median (range)	10.7 (1.3-30.3)
Glucose in CSF on day of inclusion (mg/dL), median (range)	72 (47-126)
Glucose CSF/serum ratio on day of inclusion, median (range)	0.55 (0.38-0.99)
SAPS II on day of inclusion, median (range)	47 (13-62)
SAPS II on day of exclusion, median (range)	32 (13-61)

SOFA Score on day of inclusion, median (range)	6 (1-12)
SOFA Score on day of exclusion, median (range)	2.5 (0-8)
30-day mortality	0

Table 1 Patient characteristics

CrCL: Estimated creatinine clearance (calculated using the Cockroft–Gault equation [11]); CRP: C-reactive protein; SAPS II: Simplified Acute Physiology II Score

	mean	± SD	median	95% CI
SCL (L/h)	6.11	±2.16	5.89	5.19-7.23
V_c (L)	24.33	±11.47	25.40	16.42-28.59
k_{cp} (h^{-1})	1.44	±1.22	1.18	0.61-1.86
k_{pc} (h^{-1})	2.38	±1.47	2.47	1.56-3.08
k_{cb} (h^{-1})	0.18	±0.23	0.07	0.03-0.18
k_{bc} (h^{-1})	0.12	±0.10	0.09	0.06-0.12
V_{CSF} (L)	828.51	±203.78	819.43	731.77-999.97

Table 2 Population pharmacokinetic mean and median parameters of vancomycin obtained by Pmetrics

SCL: clearance in L/h; V_c: apparent volume of distribution of the central compartment in L; V_{CSF}: apparent volume of distribution of the cerebrospinal fluid compartment in L; k_{cp}, k_{pc}, k_{bc}, k_{cb}: linear transfer rate constants in h^{-1}

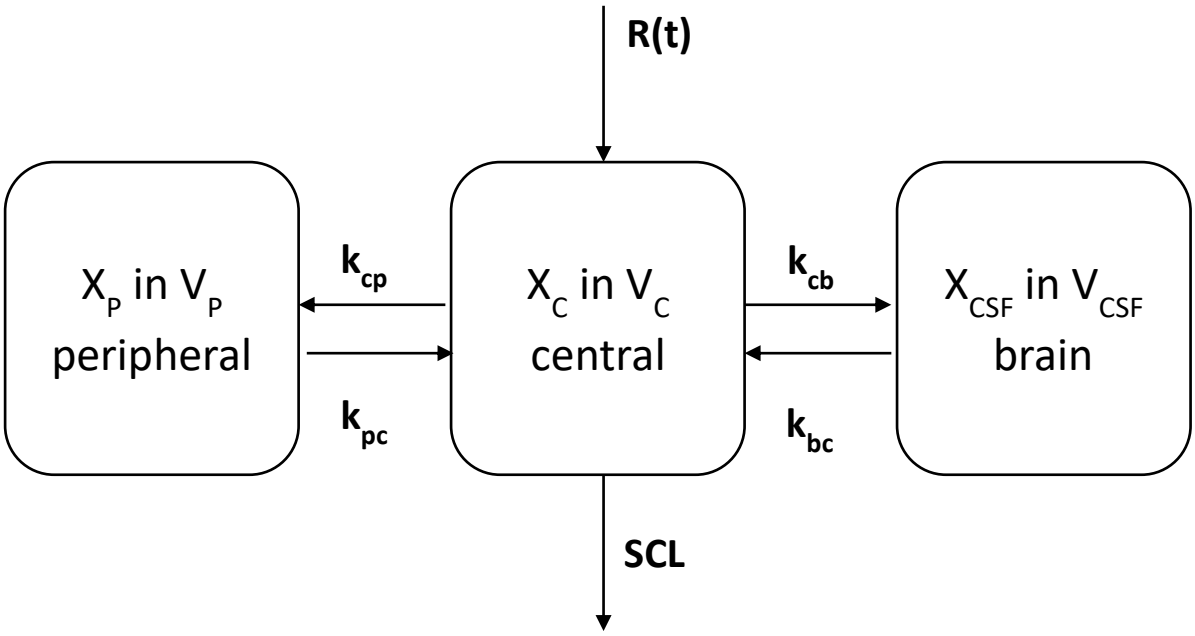
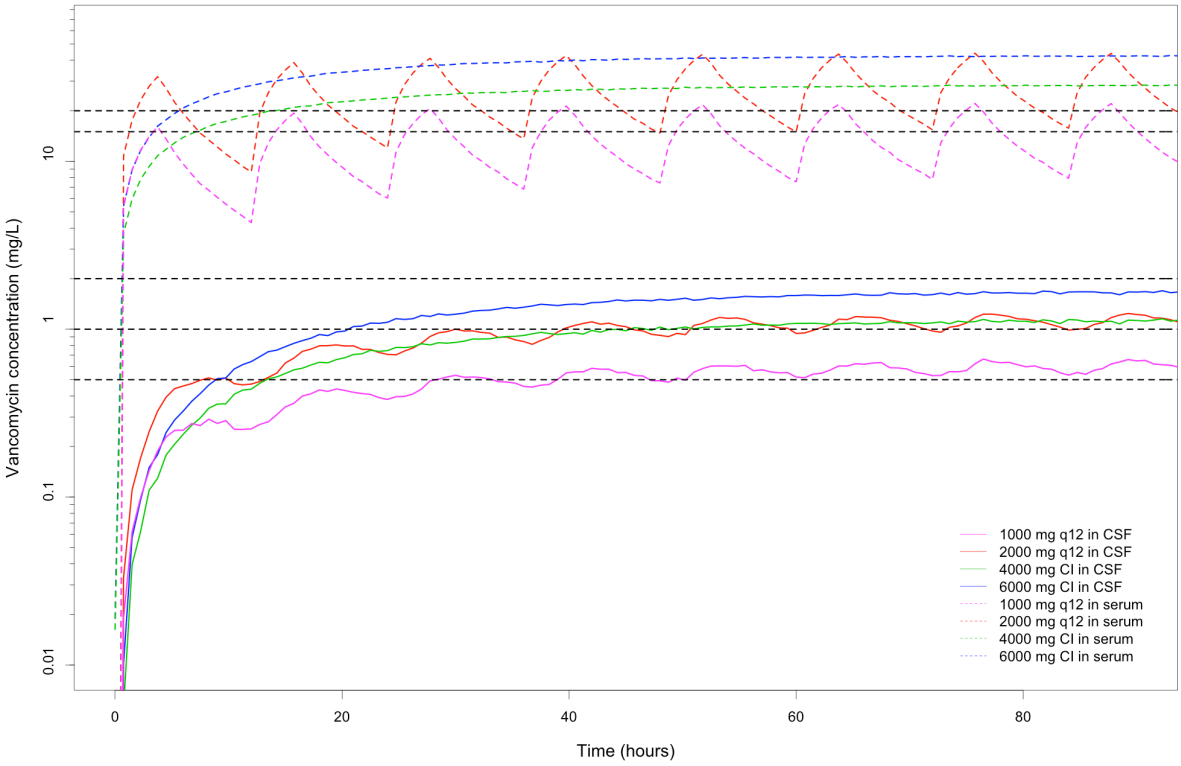


Figure 1 Structural model

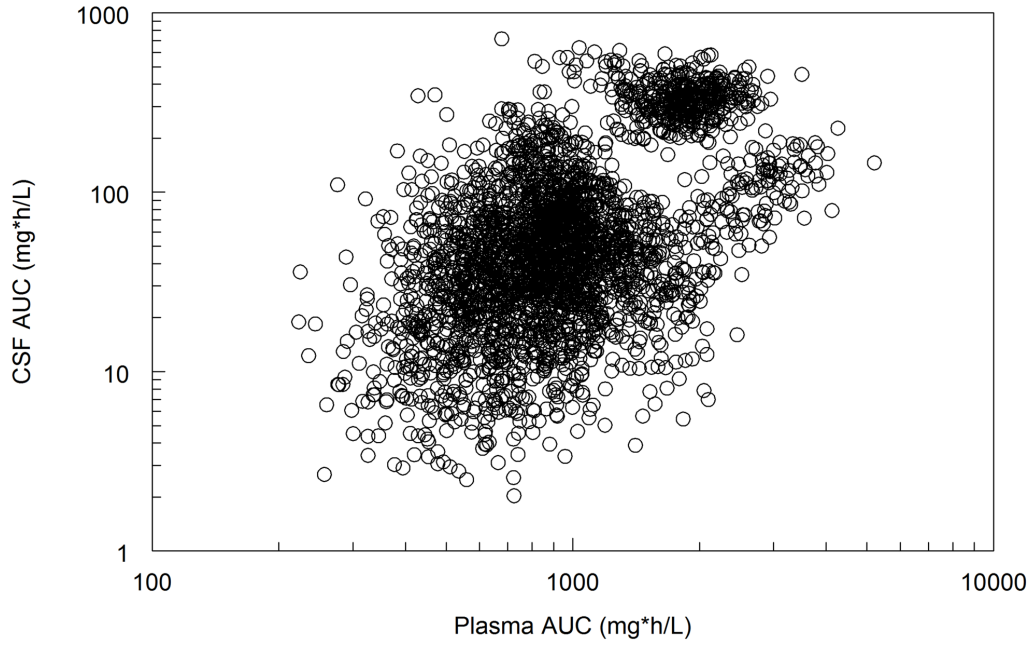
X_C is the total amount of vancomycin (mg) in the central compartment. R(t) is the zero-order-infusion of vancomycin into the central compartment (mg/h). SCL is the clearance of vancomycin from the central compartment (L/h) with a volume V_c (L). X_P is the total amount of vancomycin (mg) in the peripheral compartment with a volume V_p(L). k_{cp}, k_{pc}, k_{bc} and k_{cb} in h^{-1} represent first-order transfer constants connecting the various compartments. The CSF compartment (X_{CSF}) has an apparent CSF volume (V_{CSF}; given in litres).



425

426 **Figure 2** Comparison of different dosing regimens as prolonged infusions over 4 h or
427 continuous infusion (CI) using the pharmacokinetic model

428 Median time course of vancomycin concentrations simulated in serum and CSF over four days
429 without loading dose. Targeted vancomycin trough concentrations in CSF were 0.25 mg/L, 0.5
430 mg/L, 1 mg/L, and 2 mg/L. Targeted vancomycin trough concentration in serum were 15-20
431 mg/L for intermittent administration. This figure appears in color in the online version of *JAC*
432 and in black and white in the print version of *JAC*.



433

434

435 **Figure 3** Simulated AUC in steady-state (AUC_{0-24}) of vancomycin

436 Simulation of 3000 patients with vancomycin 1000 mg every 12 h as prolonged infusion using

437 the pharmacokinetic model.