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Vancomycin Cerebrospinal Fluid Pharmacokinetics in Children with Cerebral Ventricular Shunt Infections

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Abstract

This study described the cerebrospinal fluid (CSF) exposure of vancomycin in 8 children prescribed intravenous vancomycin therapy for cerebral ventricular shunt infection. Vancomycin CSF concentrations ranged from 0.06 to 9.13 mg/L and the CSF: plasma ratio ranged from 0 to 0.66. Two children out of three with a staphylococcal CSF infection had CSF concentrations > minimal inhibitory concentration at the end of the dosing interval.

Keywords

vancomycin; pharmacokinetics; cerebrospinal fluid; children; cerebral shunt

Cerebral ventricular shunt infections are a common cause of shunt failure and occur in 11% of children with shunts.¹ In this setting, vancomycin is the most commonly used antimicrobial drug because staphylococcal species account for nearly 75% of shunt infections.² Successful cerebrospinal fluid (CSF) sterilization depends on optimal drug exposure and, despite its widespread use, limited vancomycin CSF pharmacokinetic (PK) data are available in children. This study describes the CSF exposures of vancomycin in children with a shunt.

Methods

This was a prospective, single-center, open label PK study of intravenous (IV) vancomycin in children with suspected or documented ventricular shunt infection. Children <18 years of

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age were included if they received IV vancomycin and had CSF collected per standard care. Vancomycin dosing, infusion rate and duration of treatment were prescribed at the discretion of the treating physician. This trial was approved by the institutional review board of the Duke University Medical Center.

CSF was collected as part of standard of care through ventricular or CSF reservoir tap, if the subject had a shunt, or by lumbar puncture if no shunt was present. Vancomycin serum concentrations and dosing were retrospectively recorded from routine therapeutic drug monitoring.

Serum PK samples were analyzed by immunoassay in the Duke Hospital Clinical Laboratory using a validated assay under Good Laboratory Practice (GLP) standards. CSF PK samples were analyzed using a validated liquid chromatography–tandem mass spectrometry assay (HPLC/MS/MS).

The serum PK of vancomycin was characterized using nonlinear regression in WinNonlin v. 6.3 (Pharsight Co., St. Louis, MO). A one-compartment model with zero-order infusion was used to fit the serum PK data based on previous vancomycin PK models in children.³ The model fit was evaluated using standard model goodness of fit criteria. Vancomycin CSF penetration was measured using the ratio of CSF to serum concentrations (CSF: serum) at the same time point. Because serum and CSF concentrations (C_{serum} and C_{CSF}) were not sampled simultaneously, C_{serum} was predicted at each CSF sample time point using the following equation:

$$C_{\text{serum}} = C_{\text{max}} \times e^{(-k_e \times t)}$$

where C_{max} is the predicted maximal serum concentration; k_e the elimination constant in serum and t the time of CSF sampling. Using the same equation, serum trough concentration (C_{min}) was also predicted during the dosing interval when CSF was sampled.

As a pharmacodynamics (PD) endpoint, C_{CSF} was compared with minimum inhibitory concentration (MIC) of vancomycin for children with bacteriologically proven infection. MIC was determined by the clinical microbiology laboratory using validated broth microdilution method or Etest.

Demographics and clinical characteristics were summarized using descriptive statistics using STATA 12 (College Station, TX).

Results

Serum and CSF samples were obtained from 8 children (4 males) with a median (range) age of 4.3 years (0.2, 17), a weight of 14 kg (1, 116), and a serum creatinine of 0.42 mg/dL (0.13, 0.82) (Table 1). All children had a cerebral ventricular shunt except for one subject who had a history of external ventricular drain that was removed 7 days prior to the lumbar puncture. Among the 5 children (63%) who had a positive CSF culture, 2 had a methicillin-resistant *Staphylococcus aureus* (MRSA) (vancomycin MIC of 0.75 and 1 mg/L) and 1 had a

Staphylococcus epidermidis (vancomycin MIC of 2 mg/L). All children with confirmed infection underwent externalization of their ventriculo-peritoneal shunt and placement of an external ventricular drain. Shunt was internalized when CSF cultures were negative as decided by the treating physician. All children with confirmed infection were cured and did not have recurrent infection over a 6 month period. Of the 3 children with confirmed *Staphylococcus* sp infection, subject #2 and #8 cleared the infection after 3 days of vancomycin therapy, whereas subject #5 had persistent MRSA in CSF on day 3 and had his first negative CSF culture on day 5. The median vancomycin dose was 19 mg/kg/dose (11, 30) every 8 hours (7–13) for a mean duration of 17 days (4, 27). The median number of doses received prior to PK sampling was 47 (7–74).

Of the 8 children enrolled, one was excluded from the serum PK analysis because only a single serum sample was collected. The median number of serum and CSF samples per child was 5 (1, 14) and 2 (1, 3), respectively, resulting in a total of 43 and 12 serum and CSF samples, respectively. In serum, the median CL was 0.08 L/h/kg (0.05, 0.15), V was 0.70 L/kg (0.22, 4.46) and k_e was 0.12 /h (0.02, 0.26). The median predicted serum C_{\min} was 11.5 mg/L (3.9, 32.1).

The median C_{CSF} was 1.07 mg/L (0.06, 9.13), and CSF:serum ratio was 0.08 (0, 0.66). Visual inspection of scatter plots suggested no relationship between CSF:serum ratios and age, time after last dose, or CSF white blood cell count (data not shown). However, it appeared that CSF: serum ratio increased as CSF protein level increased (data not shown).

The 2 children with MRSA meningitis had C_{CSF} (1.15 and 9.13 mg/L) above the vancomycin MIC (0.75 and 1 mg/L) at the end of the dosing interval. The child with the *S. epidermidis* isolate had a C_{CSF} (0.06 mg/L) below the MIC (2 mg/L) 5 h after the previous dose.

Discussion

Assessment of CSF vancomycin exposure of children with shunt infection is critical because this compartment represents the drug's site of action. The range of C_{CSF} (0.06, 9.13 mg/L) in our small cohort was similar to previous studies in children (0 to 6.6 mg/L).^{4–7} A wider range of concentrations has been reported in adults (0.1, 22.3 mg/L).^{8,9} This variability could be caused by a number of factors, including different vancomycin dosing and CSF sampling times, age-related changes in blood brain barrier (BBB) and blood-cerebrospinal fluid barrier permeability, and different disease states. Limited data suggest increased drug diffusion into CNS with decreasing age.¹⁰ However, no relationship between age and CSF penetration was observed in our small cohort. In addition to maturational change, variability could be explained by difference in disease state. Inflammation associated with meningitis is thought to increase drug BBB permeability, resulting in higher CSF concentrations.¹¹ In the present study, the subject who had the highest C_{CSF} (9.13 mg/L) had elevated inflammatory markers (leukocytosis, elevated protein) in the CSF. Moreover, this same subject had the highest serum creatinine (1 mg/dL) at the time of CSF collection which could have contributed to higher vancomycin and CSF exposure due to reduced renal elimination.

Vancomycin displays time dependent activity and area under the concentration-time curve (AUC):MIC is the parameter found to best correlate with antimicrobial efficacy.¹² In adults with *S. aureus* pneumonia or bacteremia, serum AUC:MIC>400 has been associated with clinical success, and has therefore become the vancomycin PK/PD target.^{12,13} However, this serum PK/PD target has not been evaluated in patients with meningitis and its extrapolation may not be valid due to variable vancomycin penetration in CSF. Adult studies have led to recommendations of trough concentrations of at least 15 mg/L for complicated infections, if vancomycin MIC is 1 µg/mL.¹⁴ In our study cohort, serum trough concentration was < 15 mg/L in all children but 1. None of the 3 children with proven *Staphylococcus* spp infection met that target, but all cleared the infection.

The optimal method to assess vancomycin penetration into CSF is to compare AUC from both the CSF and serum compartments.^{4,15} Calculating AUC in the CSF is challenging because it requires multiple measurements of vancomycin over the dosing interval in the CSF. Because we only collected 1–3 CSF PK samples per subject, we were limited to calculating CSF:serum ratios at single time points. In the present study, distribution of vancomycin in CSF was markedly different from serum; elimination from the CSF compartment appeared to be slower than in serum allowing C_{CSF} to be more stable than C_{serum} over the dosing interval (Figure 1). This difference in PK profiles partly explains why CSF:serum ratios (0–0.66) were variable between subjects in our cohort as well as in previous reports in children (0.14 to 0.68).^{5,7} However, a previous comparison of vancomycin AUC in CSF versus serum in 6 children on vancomycin therapy resulted in an AUC CSF:serum ratio range (0.01–0.18) comparable to the ratios observed in our study.⁴

Due to our inability to estimate CSF AUC:MIC as a PK/PD endpoint, we compared C_{CSF} to the MIC for the 3 children with staphylococcal meningitis; only 2 of those achieved a C_{CSF} above the observed MIC. Despite these findings, all three children subsequently cleared the infection. Among those 3 cases of documented staphylococcal infection, we found no correlation between C_{CSF} and time to clear the infection. Subject #5 had the highest vancomycin C_{CSF} (4.79 mg/L and 9.13 mg/L), but sterilization of CSF was slightly delayed compared with the 2 other children with *Staphylococcus* sp in their CSF (5 vs 3 days).

Results from this study highlight the need to better characterize CSF vancomycin exposure. Due to different PK profiles between serum and CSF, vancomycin AUCs need to be described in both matrices and correlated to outcomes in children with *S. aureus* meningitis. This will allow the determination of an AUC:MIC target in the CSF compartment and establish a valid surrogate serum PD endpoint to guide vancomycin dosing. Children with shunt are a population with easier access to CSF, would benefit from this knowledge and should be considered as a target population in future studies.

In summary, vancomycin concentrations in CSF in our cohort of children were low but persistently detectable across the dosing interval. Penetration ratios are variable probably because of a slower clearance of vancomycin in CSF compared with serum. The CSF concentration range described in this small cohort was associated with successful therapy. Future evaluations should include prospective collection of sufficient number of serum and

CSF concentrations to allow estimation of AUC ratios, as well as documentation of clinical outcomes to better identify serum PD endpoints for shunt infection.

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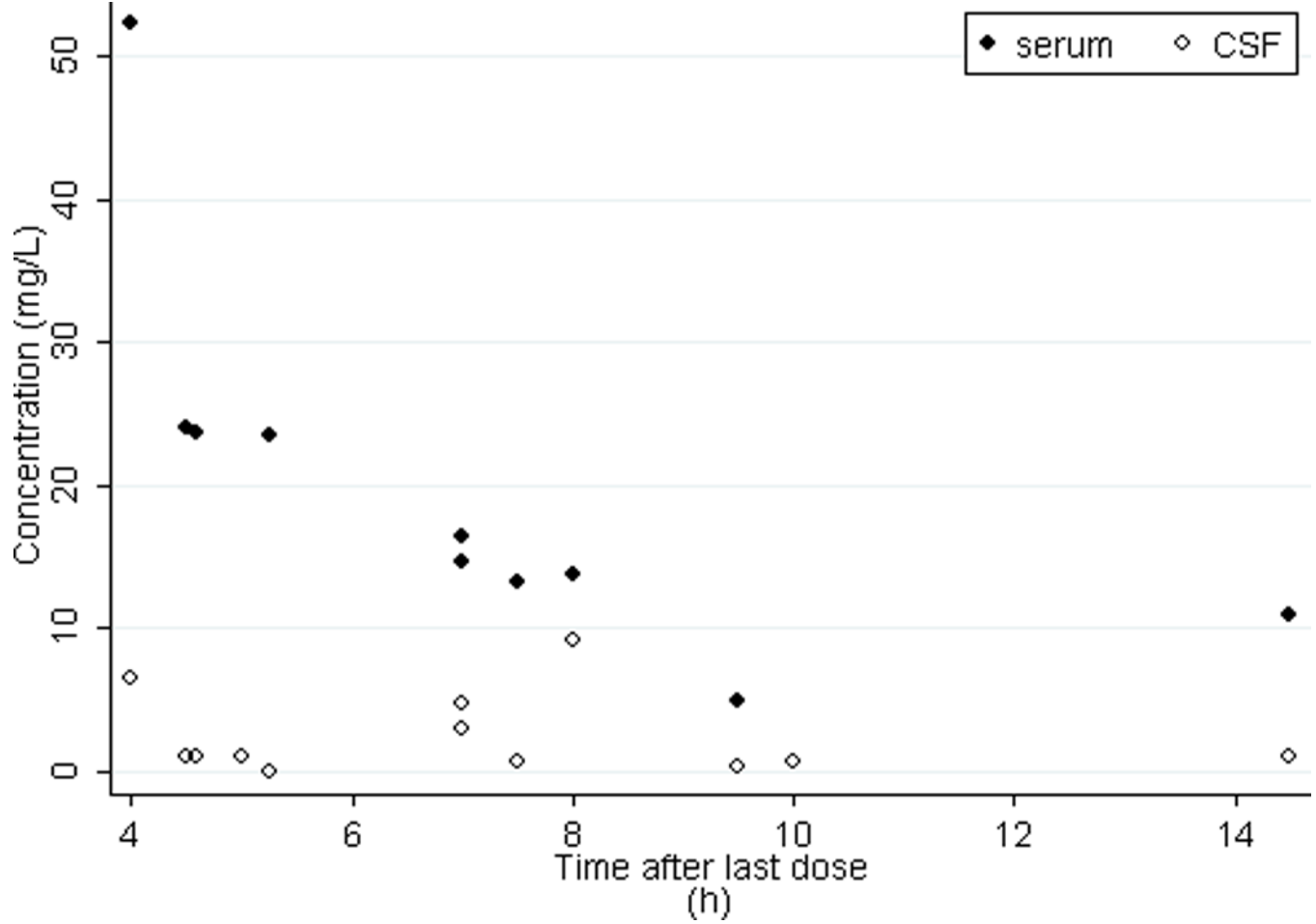


Figure 1. Vancomycin concentrations over time

CSF, cerebrospinal fluid

Two cerebrospinal fluid concentrations at 5 and 10 h are not paired with a predicted serum concentration. These concentrations are from the child who was excluded from the pharmacokinetic analysis due to insufficient serum sampling.

Table 1

Clinical characteristics and vancomycin concentrations in cerebrospinal fluid

Subject number	Age (years)	Sex	Weight (kg)	Dose* (mg/kg/dose)	Dosing interval* (h)	Days of vancomycin therapy	Serum creatinine* (mg/dL)	Ventricular CSF culture	Vancomycin MIC (mg/L)	C _{CSF} (mg/L)	Time after last dose (h)
1	0.2	M	1	30 (30, 30)	11 (8, 12)	4	0.12 (0.10, 0.20)	Negative	NA	0.98	5.0
2	0.3	F	6	18 (15, 20)	7 (4, 18)	18	0.27 (0.20, 0.40)	<i>E. coli</i>	NA	0.67	7.5
3	1.7	M	10	21 (19, 21)	8 (7, 24)	27	0.35 (0.20, 0.50)	MRSA <i>E. coli</i>	0.75 NA	1.02 1.12	4.5 4.6
4	4.3	F	12	17 (15, 20)	8 (6, 11)	8	0.22 (0.20, 0.30)	Negative	NA	0.31	9.5
5	4.4	M	17	18 (15, 21)	13 (6, 24)	23	0.69 (0.40, 1.00)	MRSA	1	4.79	7.0
6	10.4	F	30	20 (17, 22)	9 (6, 59)	23	0.51 (0.40, 0.70)	<i>Gordonia</i> sp/ <i>Rhodococcus</i> sp group	Unknown [§]	3.01	7.0
7	14.8	M	53	19 (19, 19)	8 (5, 24)	9	0.80 (0.70, 0.90)	Negative [‡]	NA	6.60	4.0
8	17.3	F	116	11 (9, 13)	7 (5, 16)	16	0.60 (0.50, 0.70)	CONS	2	0.06	5.3
Median (range)	4.3 (0.2, 17.3)	4 M (50%) **	14 (1, 116)	19 (11, 30)	8 (7, 13)	17 (4, 27)	0.43 (0.13, 0.82)			1.07 (0.06, 9.13)	7.0 (4.0, 14.5)

* mean values and range over the vancomycin therapy.

** n(%).

§ the identified bacteria was susceptible to vancomycin but the minimal inhibitory concentration was not available;

‡ CSF sampled through lumbar puncture

F indicates female; M, male; C_{CSF}, vancomycin concentration in cerebrospinal fluid; CONS, coagulase negative *staphylococcus* sp; *E. coli*, *Escherichia coli*; MIC, minimal inhibitory concentration; MRSA, methicillin resistant *Staphylococcus aureus*; NA: not applicable