Population pharmacokinetic modelling of ceftriaxone in cerebrospinal fluid in children: should we be using once or twice daily dosing for meningitis?

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Running title: PK MODELLING OF CEFTRIAXONE IN CHILDREN

Keywords: cephalosporins, dosing, meningitis, paediatrics, cerebrospinal fluid penetration, population pharmacokinetics

Synopsis

Objectives

Guidelines for bacterial meningitis in children recommend intravenous ceftriaxone 50 mg/kg (max 2 g) twice daily (BD) or 100 mg/kg (max 4 g) once daily (OD), leaving the decision regarding the dose frequency to the prescriber. We investigated the cerebrospinal fluid (CSF) penetration of ceftriaxone to evaluate whether one dosing regimen is superior.

Methods

Unbound ceftriaxone concentrations were measured in serum and CSF samples from children aged 0-18 years treated with ceftriaxone if there was sample remaining after clinical tests were performed. A serum-CSF population pharmacokinetic model was developed using non-linear mixed effects modelling. The once and twice daily dosing regimens were simulated and the probability of target attainment (PTA) determined for maintaining a CSF concentration above an MIC of 1 mg/L for common meningitis pathogens and 4 mg/L for *Staphylococcus aureus* meningitis for 100% of the dosing interval.

Results

Sixteen serum and 87 CSF samples were collected from 98 children (age range 0.1-18.5 years). The final two-compartment serum-CSF model included a renal maturation function with weight scaling on clearance, and volume of distribution. The estimated serum:CSF uptake was 20.1%. For MIC 1 mg/L, the 24-hour PTA was higher for OD (88%) compared with BD (53%) dosing, although both achieved a 100% PTA at steady state. For *S. aureus* (MIC 4 mg/L), neither dosing regimen was

sufficient.

Conclusions

Our findings support the use of a 100 mg/kg once daily regimen for empirical treatment of bacterial meningitis due to earlier achievement of the pharmacodynamic target. Neither dosing regimen was adequate for *S. aureus* meningitis.

Introduction

Bacterial meningitis is a potentially life-threatening disease in children that can lead to significant morbidity and mortality if not diagnosed and treated promptly (1). Infection can be caused by both Gram-positive and Gram-negative bacteria with the leading pathogens including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* in older children, and *Escherichia coli,* and group B streptococcus in young infants (1, 2). International guidelines recommend empirical treatment with intravenous (IV) ceftriaxone to cover most causative pathogens(1, 3, 4). This can be administered as either 50 mg/kg (max 2 g) twice daily or 100 mg/kg (max 4 g) once daily, with the decision regarding the dose frequency left to the prescriber (5, 6).

The pharmacokinetics (PK) of ceftriaxone are highly variable, influenced by disease state, renal function and critical illness (7, 8). In children, PK processes differ significantly to adults due to body size and maturation of organ function (8). Additionally, the penetration of antibiotics through the blood-brain-barrier (BBB) and into the cerebrospinal fluid (CSF) varies with age with the greatest CSF penetration occurring in infants and decreasing until the age of 4 years (9). With meningitis, inflammation of the meninges increases the permeability of the BBB (9). This interplay of disease state, age, and drug BBB penetration on the PK of ceftriaxone in the CSF has not been investigated in children and therefore, the optimal ceftriaxone dosing strategy for the treatment of bacterial meningitis in children is unknown. This study aimed to develop a population PK model of ceftriaxone in serum and CSF and using this, determine: (i) the CSF penetration of ceftriaxone in childhood; (ii) whether either once or twice daily ceftriaxone dosing is superior and should therefore be used

for the treatment of bacterial meningitis.

Results

Patient characteristics

Overall, 103 samples from 98 children were included comprising 16 serum and 87 CSF samples. Samples were collected a median of 18.4 hours (interquartile range 7.6 to 35.2, range 0.4 to 146.4) after starting ceftriaxone. The most common dosing regimen was 35 to 70 mg/kg twice daily (65/98, 66.3%), 70 to 100 mg/kg once daily (15/98, 15.3%), or a fixed dose of 1g once daily (6/98, 6.1%) or 2 g once daily (12/98, 12.2%). The median age of included children was 1.7 years (range 0.1 to 18.50), the median weight was 12.0 kg (range 3.5 to 102.3), and median creatinine level was 26 μmol/L (range 6.3 to 1897). One child had an acute kidney injury (creatinine 1897 μmol/L). Of the 98 children, approximately one-third (33, 34%) were aged between 0 to 1 year. A summary of patient demographics is presented in *Table 1***.**

Pharmacokinetic model

The final model was a two-compartment model with an additional CSF compartment, with weight scaling on central clearance and volume of distribution, and a fixed maturation effect on central clearance (*Figure S6*). Full details of the model building process, including selection of structural, statistical, and covariate models and final model code is provided in *Supplementary Material*. Observed vs predicted plots (Figure S1, S3) show no bias in prediction. No or minimal trend on residuals plots show that there was no major misspecification in the structural or the error model (Figure S3, S4, S5, S7, S9). On the prediction-corrected visual predictive check (Figure S5) plot, 95% confidence intervals of predicted concentrations overlap with

observed concentrations, suggesting adequate prediction by the model, except for slight underestimation of CSF concentrations within the first 24 h of treatment.

The model parameter estimates are provided in *Table 2*. For a population typical patient, the central clearance of ceftriaxone was estimated as 6.53 L/h/70kg, with a central volume of distribution of 17.03 L/70kg. The intercompartmental clearance between the CSF and the central compartment was low (0.0023 L/h/kg), and the estimated ceftriaxone serum:CSF penetration ratio was 20.1%. CSF inflammatory markers including WCC, protein and glucose levels did not improve model fit as a covariate for serum:CSF penetration.

Evaluation of ceftriaxone 50 mg/kg twice-daily versus 100 mg/kg daily dosing

A total of 1000 patients aged between 0 to 18 years were simulated. The simulated ceftriaxone CSF concentration vs time plots are presented in Figure 1. Regardless of the dosing regimen, an initial CSF distribution phase of approximately 3 hours was observed following the first dose. After this time, the CSF ceftriaxone concentration remained relatively constant. A median CSF concentrations of approximately 5.6 mg/L and 6.6 mg/L at 72 to 96 hours and 168 to 192 hours after the start of treatment was observed for both regimens, although large inter-individual variability was observed (Figure 1).

The PTA of achieving 100%T>MIC for the target MIC values is shown in Figure *2*. For an MIC of 1 mg/L covering the most common pathogens causing meningitis, the PTA of achieving the PD target of 100%T>MIC during the first 2.5 to 24 hours of treatment, was 53% with twice-daily dosing in comparison to 88% with once-daily

dosing. However, at 72 to 96 hours and 168 to 192 hours, both regimens achieved 100%T>MIC. For an MIC of 4 mg/L for *S. aureus*, the PTA was 0 for both regimens from 2.5 to 24 hours. At 72 to 92 hours, this increased to 63% and 58% for twice- and once-daily dosing, respectively, and at 168 to 192 hours 75% and 69%, for twice- and once-daily dosing, respectively.

Discussion:

To our knowledge, this is the first model to describe the PK of ceftriaxone in the CSF of children. Our findings support the use of a 100 mg/kg once-daily dosing regimen for empirical treatment of bacterial meningitis in children due to earlier attainment of the PK/PD target 2.5 hours after the first dose as well as the higher %T>MIC with increasing MIC values (Figure 2). This dosing regimen is in line with the current National Institute for Health and Care Excellence (NICE) and the Infectious Disease Society of America (IDSA) guidelines (3, 6). For pathogen-directed treatment of meningitis, both the once and twice-daily dosing regimens achieved a 100% PTA for bacteria with a MIC susceptibility breakpoint of ≤1 mg/L including *S. pneumoniae*, *N. meningitidis,* and *H. influenzae, E.coli* and other Enterobacterales (10). For *S. aureus* meningitis, neither ceftriaxone dosing regimen adequately achieved the PK/PD target and therefore, should not be used for this indication.

Currently, a consensus PK/PD target for ceftriaxone for treatment of bacterial meningitis is lacking (11). Simulation studies have demonstrated that attaining a 100%T>MIC would achieve a desired 50% T>4×MIC, the latter being another commonly used PK/PD target for efficacy (12, 13). In other studies of cephalosporins (cefepime and ceftazidime), an increasing %T>MIC was associated with higher bacterial eradication and 100%T>MIC increased the chance of clinical cure and bacterial eradication (14). Therefore, the 100%T>MIC target was chosen for this study. To date, there have been no published clinical studies comparing the clinical efficacy of different dosing regimens of ceftriaxone for meningitis and therefore, it is unclear whether these findings translate to differences in clinical outcomes. However, once-daily dosing regimens provide several other advantages including reduced line

access and ease of outpatient parenteral antibiotic administration.

A potential reason for the higher CSF penetration with once daily dosing is the higher serum:CSF concentration gradient (15, 16). These findings are consistent with the NeoMero study that found that compared to continuous infusions of meropenem, bolus dosing had a higher CSF %T>MIC (17). Interestingly, age and CSF inflammatory markers were not found to be significant covariates for CSF penetration of ceftriaxone. This could potentially be due to ceftriaxone's relatively high lipophilicity which facilitates its diffusion across the BBB irrespective of maturation (9). The serum:CSF penetration ratio of 0.201 in our study is similar to a study in adults which reported a ratio is 0.144 (17).

Most ceftriaxone PK modelling studies estimate unbound concentrations through its saturable protein binding kinetics where the fraction of unbound ceftriaxone increases with total ceftriaxone concentration (17–20). However, as only the unbound ceftriaxone penetrates the BBB (9), these concentrations were used for our PK model development. Using this approach, our model estimates were comparable to another study in adults that reported a central clearance of 6.54 L/h/70kg and volume of distribution of 13.8 L/70kg (21). However, unlike the study in adults, serum creatinine was not found to be a significant covariate in our model which may partly be explained by the inclusion of a maturation model for clearance.

Limitations of this study are that both serum and CSF samples to determine ceftriaxone concentrations were taken opportunistically using remaining clinical sample after clinical testing was performed. Therefore, the timing of samples was not

optimised, accuracy of the documentation of the timing of samples cannot be confirmed, and the dataset was sparse. As a result, the study's model building was confined to only estimating interindividual variability in central clearance that limited accuracy of the estimates of other parameters. The final model estimates on central clearance had high shrinkage of > 41%, which limited the identification of further covariates (22). As a result, the interindividual variability on central clearance remained high (%CV = 63.1) similar to values reported in an adult study (17). In addition, most children in this study had a normal CSF WCC and protein. It is likely that in the presence of meningeal inflammation, the CSF penetration of ceftriaxone would differ.

Conclusions

In conclusion, our findings support the use of a 100 mg/kg once-daily dosing regimen for empirical treatment of bacterial meningitis in children due to earlier achievement of the PD target. Neither dosing regimen achieved adequate CSF concentrations for treatment of *S. aureus* meningitis. Future studies should focus on evaluating the impact of these PK differences on clinical outcomes.

Materials and Methods

Data and sample collection:

Serum and CSF samples for PK analysis were prospectively collected from children aged 0 to 18 years admitted to RCH Melbourne, a major tertiary paediatric referral hospital in Victoria, Australia. Samples were included if:

(i) a CSF and/or serum sample was taken from a child during the study period (Feb 2017 to May 2021);

(ii) ≥200 µL of CSF and/or serum was available after the requested clinical tests were performed and;

(iii) the samples were collected after the administration of ceftriaxone.

This study was approved by The Royal Children's Hospital (RCH) Human Research Ethics committee (HREC 36332) with a waiver for consent.

At RCH, institutional guidelines recommend ceftriaxone for suspected bacterial meningitis in children aged 2 months or above. It is administered as a 30-minute IV infusion for doses >50 mg/kg, as an IV bolus over 5 minutes for doses ≤50 mg/kg, or over 60 minutes for neonates less than 28 days of age (5).

After collection, serum and CSF samples were frozen at -80^{o}C and transported on dry ice to Pathology Queensland for determination of unbound ceftriaxone concentrations using an ultracentrifugation method with an Amicon Ultra 0.5ml 30,000-molecular-weight-cutoff centrifugal filter device (Merck Millipore, Sydney, AUS). Ceftriaxone concentrations were quantified using an Ultra Performance Liquid chromatography coupled with QDa mass detection (Waters Corporation, Milford, MA, USA). The lower limit of quantification (LLOQ) was 0.1 mg/L, and the imprecision was <10% at

all levels.

Data on the ceftriaxone dosing regimen and concentrations in CSF and serum as well as other relevant patient characteristics affecting drug PK (postnatal age (PNA), sex, postmenstrual age (PMA), serum creatinine (SCr), albumin, and weight (WT)) were collected. As inflammation of the BBB has been shown to affect the CSF penetration of drugs (23, 24), CSF inflammatory markers, including white cell count (WCC), protein and glucose levels were also collected.

Data analysis and PK model development:

Raw data processing was conducted using R (version 4.2.0). Concentration values below the lower limit of quantification were replaced with half the lower quantification limit. The PK model was developed using the non-linear mixed effects modelling package nlmixr2 (ver. 2.1.1) and dosing simulation in rxode2 (ver. 2.1.2), both being open-source packages based in R.

Non-linear mixed effects modelling with first-order conditional estimation with interaction (FOCEI) method was used to develop the PK model. Model building started with the serum data alone (serum model): one- and two- compartment models were tested to determine the basic structural model. Since only unbound ceftriaxone distributes into the CSF, unbound ceftriaxone alone was modelled. Log-normal inter-individual variability (IIV) was assumed. For the statistical model, additive, proportional, and combined residual error models were evaluated. Likelihood ratio test and Akaike information criterion were used to choose between nested and non-

nested models, respectively. Standardised weight scaling on central clearance (CL), intercompartmental clearance, central volume (V) and peripheral volume, and a postmenstrual age (PMA) maturation sigmoidal function on CL were added to the model *a priori* (Equation 1 & 2).(25) Covariates for the CSF model were tested in a forward stepwise method based on a likelihood ratio test. Covariates were included if there was a reduction in the objective function value of greater than 3.84 units corresponding to a p-value of <0.05.

Once the unbound serum model was finalised, a CSF compartment was added. Considering the relatively sparse CSF dataset, the CSF volume was fixed as 150 mL and scaled for body weight (26). Additional CSF inflammation markers (white cell count, protein and glucose) were evaluated as covariates for the serum:CSF model using the same method as for the serum model. The final model therefore described unbound ceftriaxone concentrations in serum and CSF.

$$Equation\,1: CL_i = CL_{pop} \cdot \left(\frac{WEIGHT_i}{70\,Kg} \right)^{0.75} \cdot \frac{PMA^{Hill}}{PMA_{50}^{Hill} + PMA^{Hill}}$$

$$Equation\,2: V_i = V_{pop} \cdot \left(\frac{WEIGHT_i}{70\,Kg} \right)^{1}$$

Dose simulation:

The final serum-CSF model was used to simulate the two recommended dosing regimens for bacterial meningitis: 50 mg/kg twice daily, and 100 mg/kg daily, with a maximum dose of 4 g/day (6). Patient groups were generated based on the British

National Formulary's reference bodyweight per age group (27). A primary MIC target of 1 mg/L was selected based on the European Committee for Antimicrobial Susceptibility (EUCAST) recommendation which covers the MIC breakpoints for the most common bacterial causes of meningitis (*S. pneumoniae* MIC 0.5 mg/L, *N. meningitis* MIC 0.125 mg/L, *H. influenzae* MIC 0.125 mg/L, *E. coli* MIC 1 mg/L (10). In addition, the EUCAST MIC for susceptible *S. aureus* of 4 mg/L was also evaluated (10).

As ceftriaxone exhibits time-dependent killing, the PK/pharmacodynamic (PK/PD) target was the fraction of time (%T) the unbound ceftriaxone concentration exceeded the target MIC (%T >MIC) during a dosing interval in CSF. A 100%T>MIC was selected as the PK/PD target based on previous studies showing that a high %T>MIC correlated with maximal antibacterial effect (12, 13). As CSF concentrations of antibiotics have been shown to gradually increase after a first antibiotic dose as a result of diffusion, attainment of the PK/PD target was evaluated from 2.5 to 24 hours, 72 to 96 hours and 168 to 192 hours to compare the probability of target attainment (PTA) of the two dosing regimens achieving the PK/PD target of 100%T>MIC for simulated patients at the start of therapy and at steady state (28, 29).

Supplement Material

Supplementary material accompanies this paper on the Journal of Antimicrobial Chemotherapy website. Supplementary methods, Supplementary results, Figures S1-S5, and Ceftriaxone nlmixr2 PK model code.

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Conflict of interests

The authors declare no conflict of interests.

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Figure Captions:

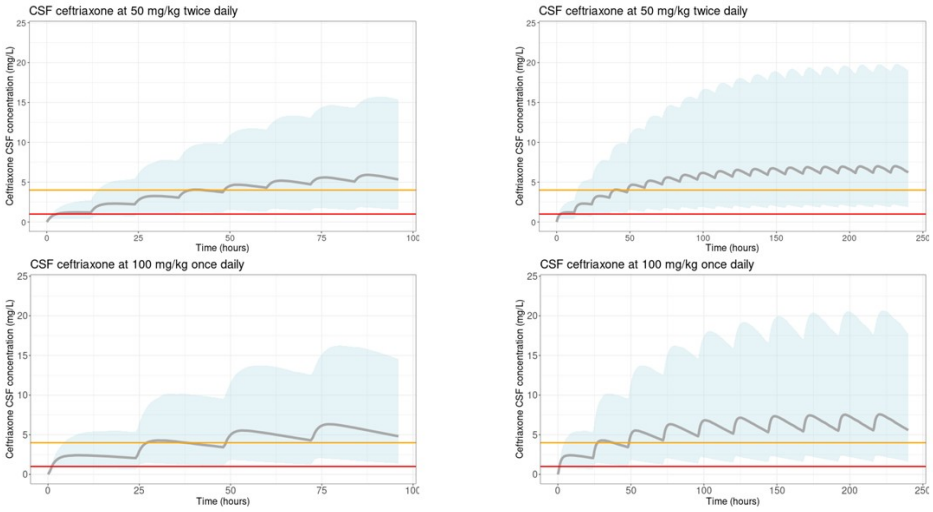


Figure 1: CSF ceftriaxone concentrations versus time plot in simulated patients. Middle line indicates median CSF ceftriaxone concentration of simulated patients and shaded area indicates CSF ceftriaxone concentration in 95% of simulated patients.

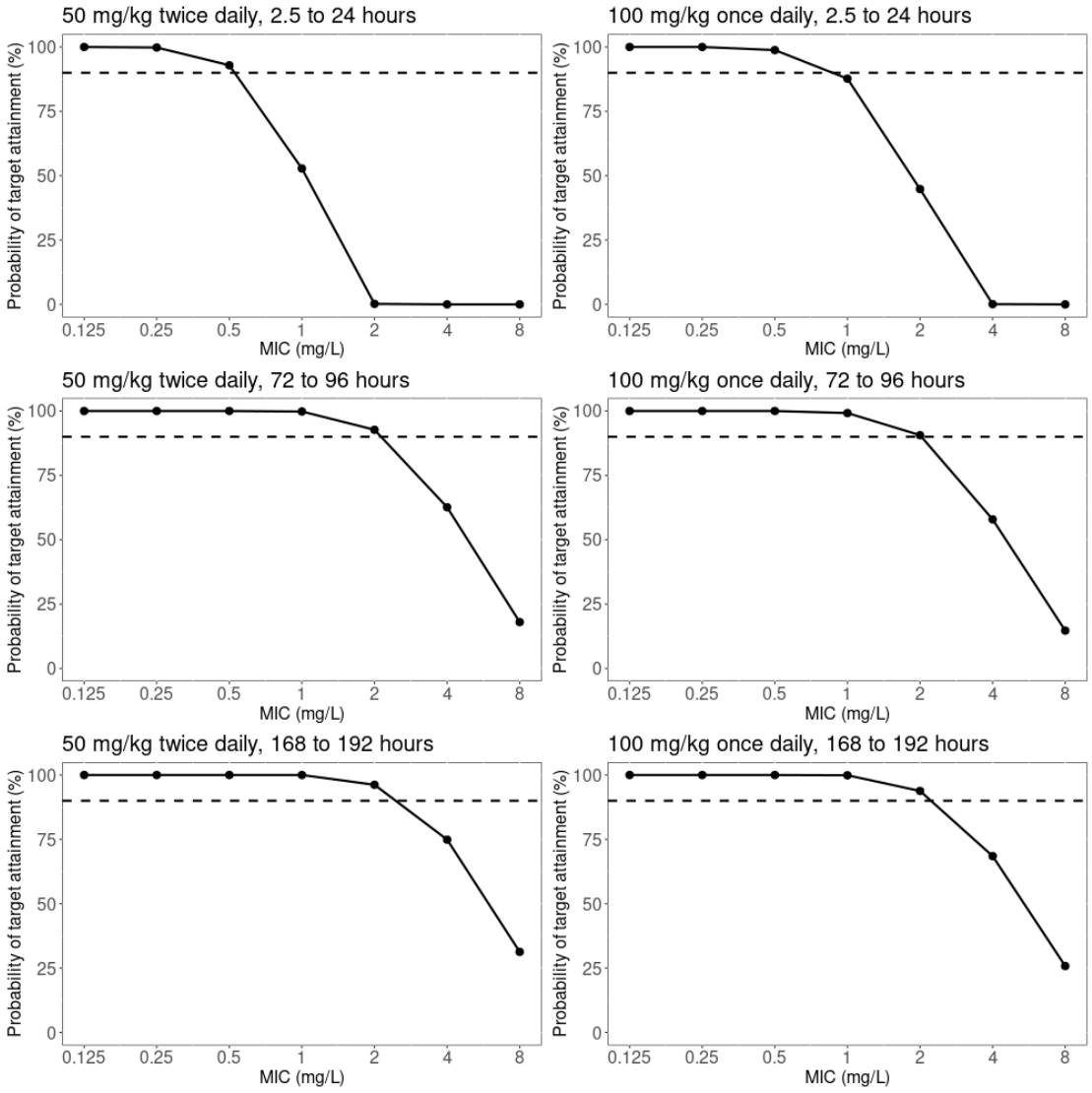


Figure 2: Probability of target attainment (100% T>MIC) in cerebrospinal fluid with increasing target MICs, which is shown in the first 2.5-24 hours, at 72 to 96 hours and 168 to 192 hours after the start of treatment.

Tables:

Table 1: Summary of patient demographics. A total of 98 patients were included in the study.

No. of Patients	**All patients (n=98)**	**Patients with serum concentrations (n=16)***	**Patients with CSF concentrations (n=83)***
	Number (Percentage)		
0 - <1 years	33 (33.7%)	3 (18.8%)	30 (36.1%)
1 - 18 years	65 (66.3%)	13 (82.2%)	53 (63.9%)
Characteristics	**Median (Range)**		
Age (years)	1.7 (0.1 – 18.5)	4.6 (0.2 – 18.5)	1.4 (0.1 – 16.3)
Weight (kg)	12.0 (3.5 – 102.3)	18.8 (6.3 – 58)	11.1 (3.5 – 102.3)
Gender (M/F)	58 / 40	10 / 6	48 / 35
Dose/Weight (mg/kg)	50.0 (9.8 – 100.2)	50.0 (17.2 – 100.0)	50.0 (9.8 – 100.2)
Lab tests	**Median (Range)**		
Serum Creatinine (µmol/L)	26.0 (6.3 – 1897)	29.0 (17 – 79)	26.0 (6.3 – 1897)
Albumin (g/L)	34.0 (20 – 51)	33.0 (20 – 46)	34.0 (21 – 51)
CSF WCC (× 106/L)	3.0 (0 – 945)	3.0 (3 – 3)	3.0 (0 – 945)
CSF Protein (g/L)	0.21 (0.05 – 2.39)	0.21 (0.12 – 0.21)	0.21 (0.05 – 2.39)
CSF Glucose (mmol/L)	3.3 (0.55 – 7.1)	3.3 (3.2 – 3.3)	3.3 (0.55 – 7.1)

*One patient provided both serum and cerebrospinal fluid (CSF) sample and is included in both groups in this table.

Table 2: Parameter estimates of final serum-CSF model. CI – confidence interval; CV – coefficient of variation; CSF – cerebrospinal fluid; h – hour kg – kilogram; L – litre; RSE – residual squared error.

Parameter		**Estimates (95%CI)**	**%RSE**	**%CV**	**%Shrinkage**
Serum Compartment					
Central clearance (CL_{pop})	L/h/70kg	6.53 (4.71, 9.05)	8.9	63.1	41.6
Central volume (V_{pop})	L/70kg	17.03 (11.44, 25.35)	7.2		
Intercompartmental clearance ($Q2_{pop}$)	L/h/70kg	1.60 (0.71, 3.60)	88.6		
Peripheral volume ($V2_{pop}$)	L/70kg	26.21 (7.31, 93.97)	19.9		
Proportional error		0.209			
CSF Compartment					
CSF-central intercompartmental clearance ($Qcsf_{pop}$)	L/h/70kg	0.0024 (0.0003, 0.019)	17.5		
CSF volume ($Vcsf_{pop}$)	L/70kg	FIXED to 0.15	FIXED	N/A	
CSF uptake ratio (uptk)		0.201 (0.059-0.686)	39.0		
CSF additive error		2.15			

Model equations:

$$CL_{\square} = CL_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg} \right)^{0.75} \cdot \frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}} \cdot e^{n}, V = V_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg} \right)$$

$$Q2 = Q2_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg} \right)^{0.75}, V2 = V2_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg} \right)$$

$$Qcsf = Qcsf_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg} \right)^{0.75}, Vcsf = Vcsf_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg} \right)$$

$$k = CL/V, k12 = Q2/V, k21 = Q2/V2, k13 = Qcsf \cdot uptk/V, k31 = Qcsf/Vcsf$$

$$\frac{dA1}{dt} = -k \cdot A1 - k13 \cdot A1 + k31 \cdot CSF - k12 \cdot A1 + k21 \cdot A2$$

$$\frac{dA2}{dt} = k12 \cdot A1 - k21 \cdot A2$$

$$\frac{dCSF}{dt} = k13 \cdot A1 - k31 \cdot CSF$$

Population pharmacokinetic modelling of ceftriaxone in cerebrospinal fluid in children: should we be using once or twice daily dosing for meningitis?

Supplement materials

Supplementary methods - model evaluation:

The final model was evaluated using goodness of fit (GOF) plots. The model's individual prediction (IPRED) and population prediction (PRED) values were plotted against observed values. An ideal model should yield predictions in line with observations, whereas population deviations were indicative of parameter and observation level variability and individual deviations were indicative of model residual variability. Conditional weighed residual (CWRES) was plotted against time after last dose (TAD). The interpretation of the CWRES distribution was interpreted for structural model plausibility, where an ideal model should have CWRES following a normal distribution of N ~ (0, 1) and distribute within two standard deviations away from the median of zero and with no trend in their values. Additionally, the model's statistical model was evaluated by plotting individual weighted residual (IWRES) against IPRED. The trajectory of IWRES vs. IPRED was indicative of statistical model selection, where an increasing IWRES suggested proportional error instead of additive.

Prediction-corrected visual predictive check (VPC) facilitates the assessment of the appropriateness of the model to the data by simulating from the model. An ideal model should yield VPC plots where observed data follow the distribution of simulated data, i.e., the median and 5th and 95th percentiles of observed data should be close to the respective values of simulated data. Prediction correction corrects for the differences due to independent variables (e.g., time, dose, or any covariate values).

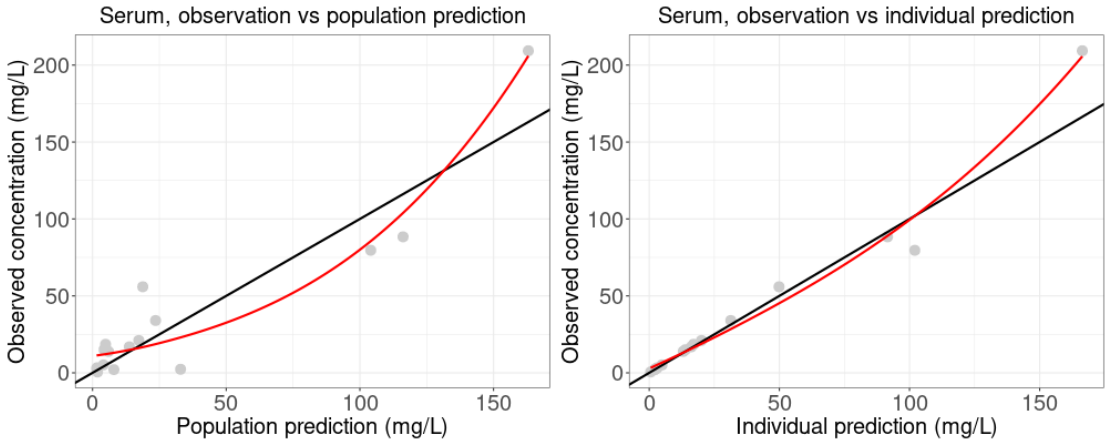


Figure S1. PRED ~ Observation plot (left) and IPRED ~ Observation plot (right) in the serum model. Red line shows trend in observations and black line identity line.

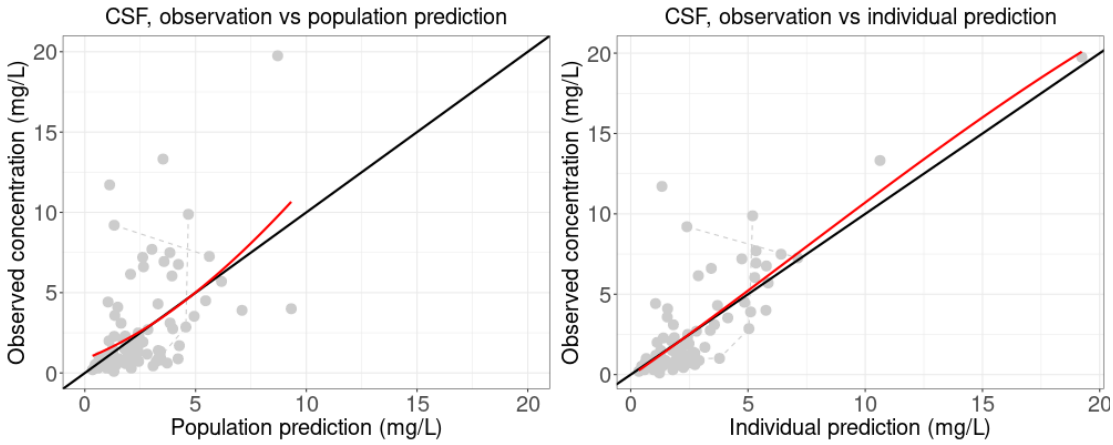


Figure S2. PRED ~ Observation plot (left) and IPRED ~ Observation plot (right) in the CSF model. Red line indicates trend in observations and black line identity line. Dashed grey lines connect concentrations from the same patient.

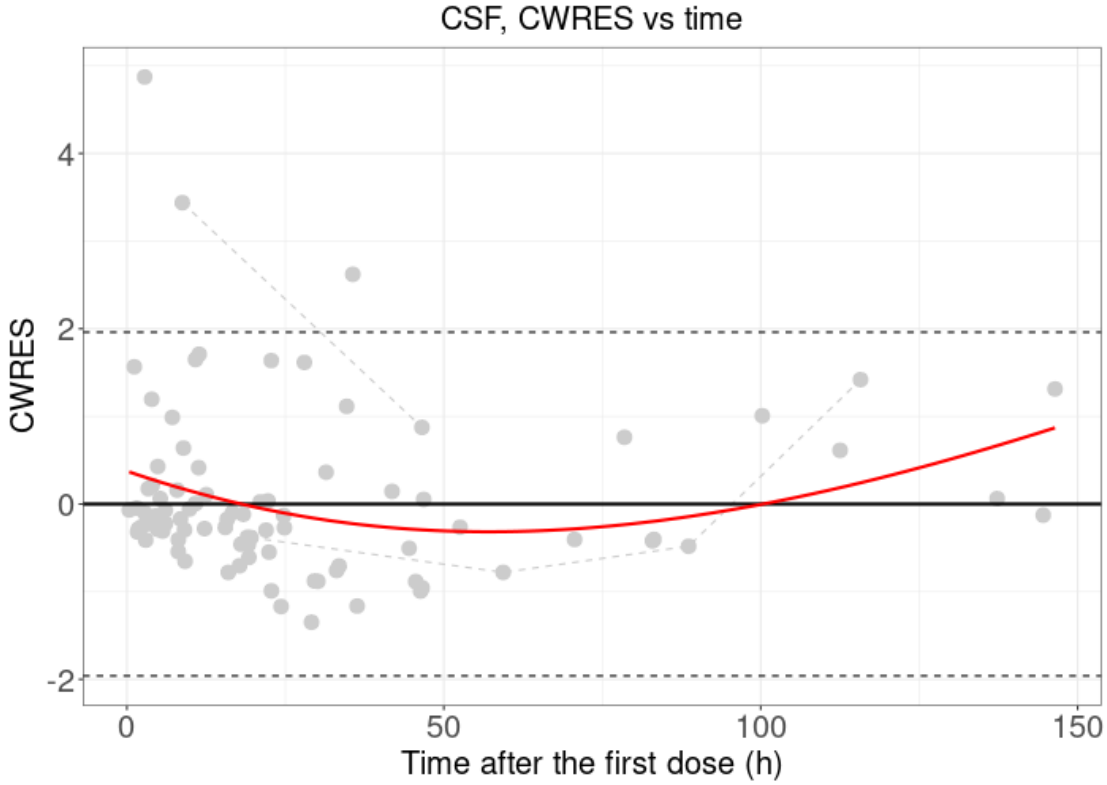


Figure S3. CWRES of CSF compartment prediction plotted against time after the first dose

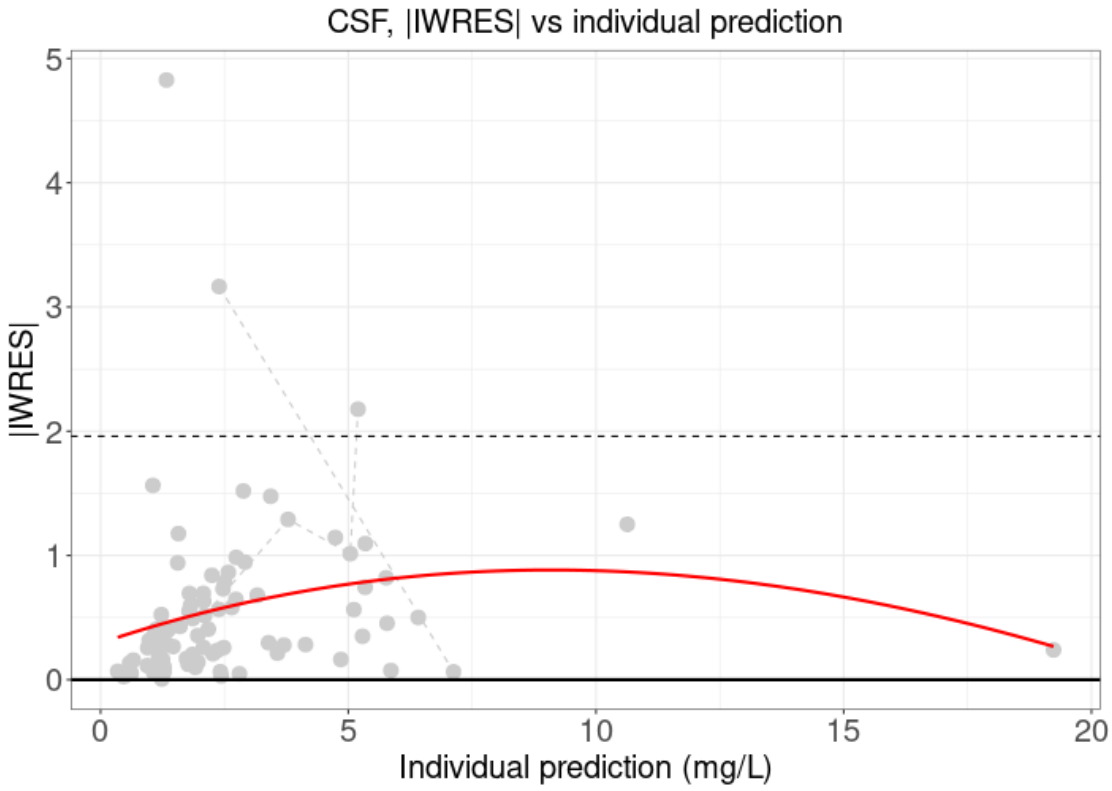


Figure S4. IWRES ~ Individual plots.

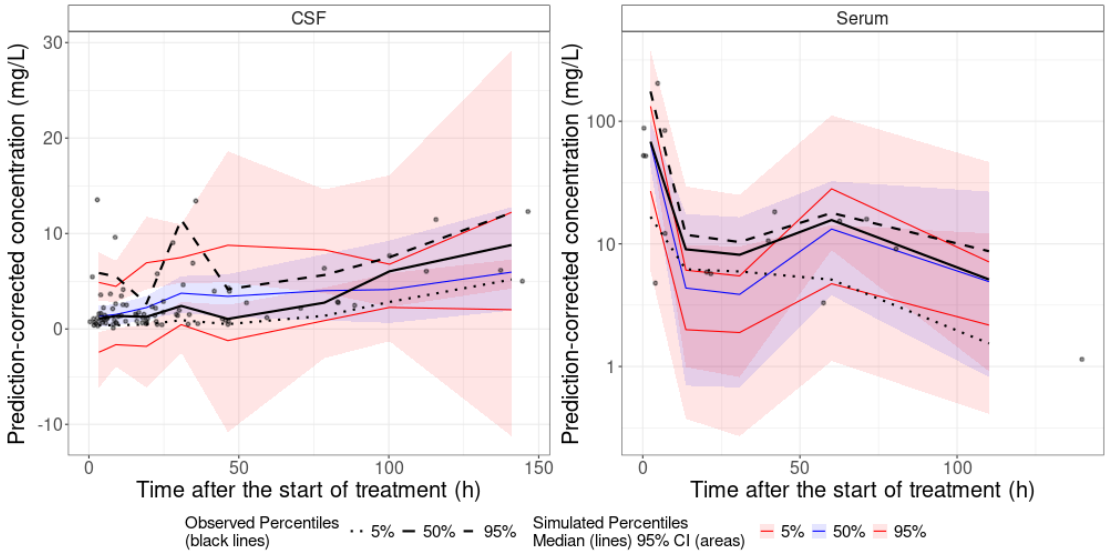
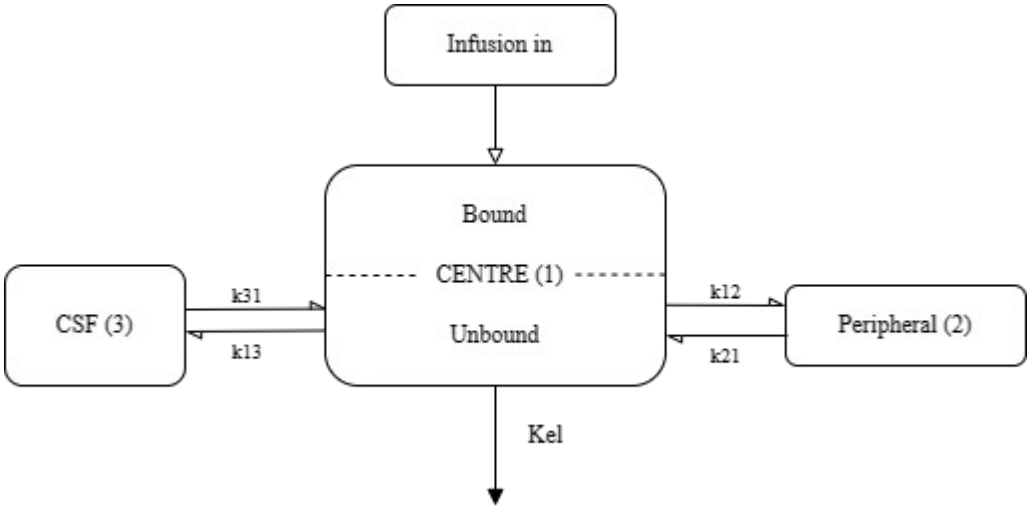


Figure S5. Prediction-corrected visual predictive check of cerebrospinal fluid (CSF) and serum data. Blue line shows the 50th percentile of simulated data and red lines the 5th and 95th percentiles. Shaded areas represent the 95% confidence intervals of the respective predicted percentiles. Solid black line represents the 50th percentile of observed data, dotted black line the 5th percentile and dashed black line the 95th percentile. Observed concentrations are represented by points.

Supplementary results:



$$CL_{\square} = CL_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg}\right)^{0.75} \cdot \frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}} \cdot e^{n}, V = V_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg}\right)$$

$$Q2 = Q2_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg}\right)^{0.75}, V2 = V2_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg}\right)$$

$$Qcsf = Qcsf_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg}\right)^{0.75}, Vcsf = Vcsf_{pop} \cdot \left(\frac{WEIGHT}{70\,Kg}\right)$$

$$k = CL/V, k12 = Q2/V, k21 = Q2/V2, k13 = Qcsf \cdot uptk/V, k31 = Qcsf/Vcsf$$

$$\frac{dA1}{dt} = -k \cdot A1 - k13 \cdot A1 + k31 \cdot CSF - k12 \cdot A1 + k21 \cdot A2$$

$$\frac{dA2}{dt} = k12 \cdot A1 - k21 \cdot A2$$

$$\frac{dCSF}{dt} = k13 \cdot A1 - k31 \cdot CSF$$

Figure S6. Schematic representation of final model and model equations. Only unbound ceftriaxone was modelled

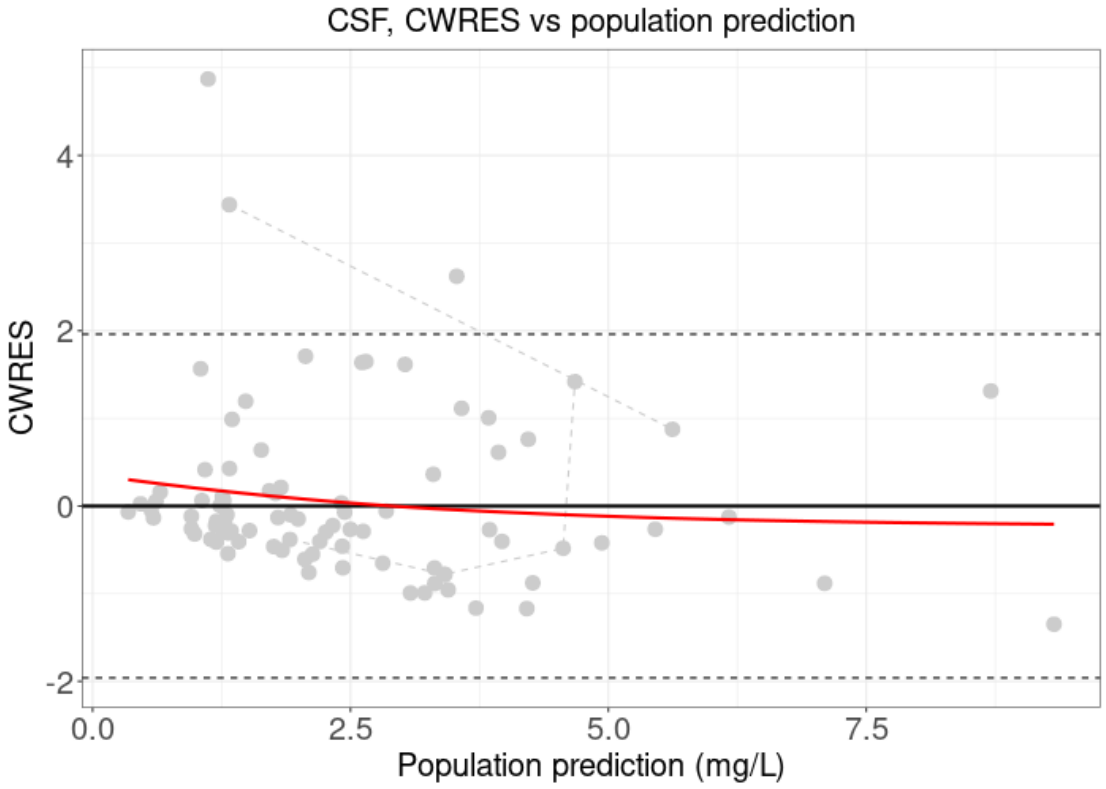


Figure S7. Conditional weighted residuals (CWRES) vs population predictions in cerebrospinal fluid (CSF) compartment.

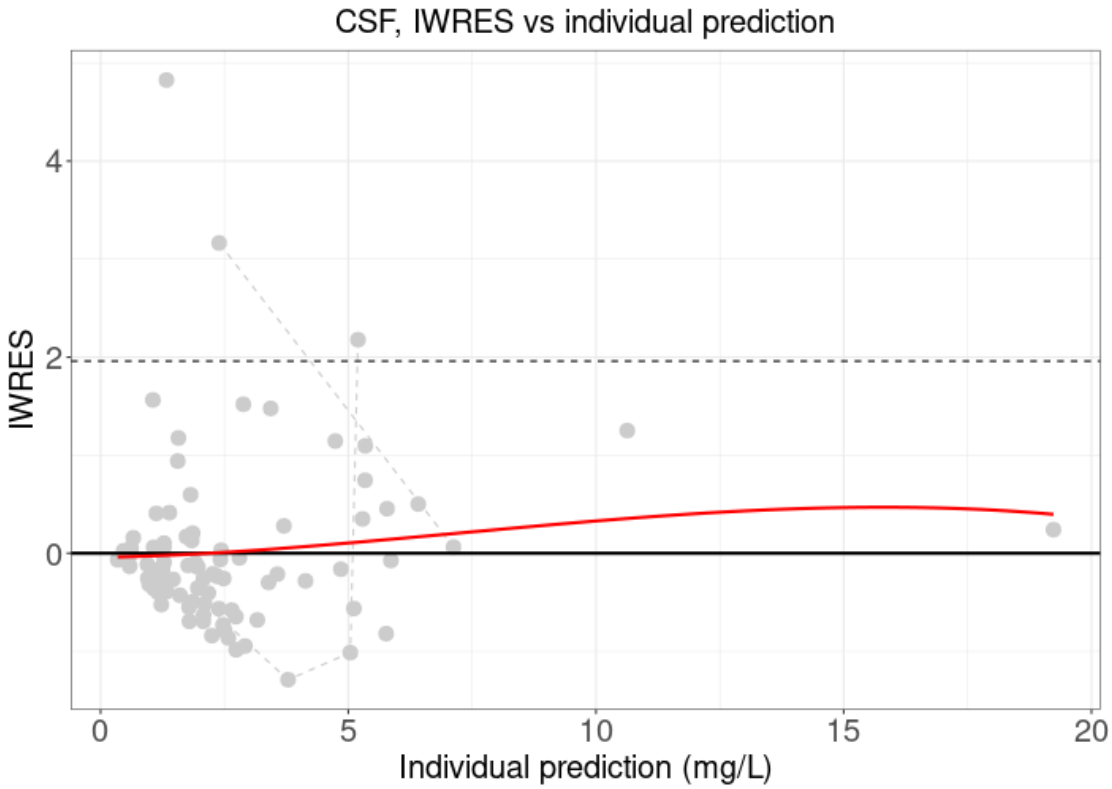


Figure S8. Individual weighted residuals (IWRES) vs individual predictions in cerebrospinal fluid (CSF) compartment.

Table S1. Selection of the final population pharmacokinetic model for the serum data

	rror model	Objective function value	Akaike information criterion
One-compartment model*	Proportional	108.93	146.34
One-compartment model*	Additive	109.21	146.61
One-compartment model*	Combined	104.65	144.06
Two-compartment model*	Proportional	91.25	132.66

Two-compartment model*	Additive	93.59	135.00
Two-compartment model*	Combined	91.23	134.63

*Both models included allometric scaling for size of clearance, intercompartmental clearance and volumes of the compartments and maturation function of clearance. Only clearance included interindividual variability.

Table S2. Selection of the final population pharmacokinetic model for the cerebrospinal fluid data, after finalizing the model for the serum data

	Objective function value	Akaike information criterion
Base model*	342.44	549.74
Add protein as covariate for uptake to CSF	344.09	553.39
Fix CSF-serum intercompartmental clearance to 0.017 L/h/70kg	354.23	559.53

*Cerebrospinal fluid (CSF) compartment added to the two-compartment serum model with uptake parameter and CSF-serum intercompartmental clearance parameter estimated, volume of CSF fixed to 0.15 L/70kg and additive error model used.

Final model nlmixr2 codes:

```
library(nlmixr2)
library(knitr)
library(ggplot2)


two_cmt_prop_AS_mat_CSF_add <- function() {
  ini({
    tcl <- log(6)                    # L/h/70kg
    tv  <- log(20)                   # L/70kg
    tq2 <- log(4.5)                  # L/h/70kg
    tv2 <- log(20)                   # L/70kg

    tqcsf <- log(0.02)               # L/h/70kg
    tvcsf <- fix(log(0.15))          # L/70kg (FIXED)

    tUPTK <- c(-Inf,log(0.19),log(1))

    eta.cl ~ 0.1
    eta.v  ~ fix(0)
    eta.q2 ~ fix(0)
    eta.v2 ~ fix(0)
    eta.qcsf ~ fix(0)

    prop.err <- 0.5
    add.csf <- 0.5
  })
  model({

    log_WT ← log(WEIGHT/70)
    cl <- exp(tcl + eta.cl + 0.75 * log_WT) * PMA^3.4 /
(47.7^3.4 + PMA^3.4)
    v  <- exp(tv + eta.v + log_WT)
    q2 <- exp(tq2 + eta.q2 + 0.75 * log_WT)
    v2 <- exp(tv2 + eta.v2 + log_WT)

    qcsf <- exp(tqcsf + eta.qcsf + 0.75 * log_WT)
    vcsf <- exp(tvcsf + log_WT)

    uptk <- exp(tUPTK)

    k <- cl / v           # elimination rate constant
    k12 <- q2 / v
    k21 <- q2 / v2
    k13 <- qcsf * uptk / v
    k31 <- qcsf / vcsf

    d/dt(A1) = - k * A1 - k13 * A1 + k31 * CSF  - k12 * A1 +
k21 * A2
    d/dt(A2) =   k12 * A1 - k21 * A2
    d/dt(CSF) =  k13 *A1 - k31 * CSF

    serum = A1 / v                          # concentration in
```

```
serum
    serum ~ prop(prop.err)                    # error model
    csf = CSF / vcsf                          # concentration in
CSF
    csf ~ add(add.csf)                        # error model
  })
}
```