

CSF and Plasma Pharmacokinetics of Naproxen in Children

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Objectives

The objective of this study was to assess the pharmacokinetics of naproxen in children aged 3 months to 13 years and to quantify the cerebrospinal fluid (CSF) permeation of naproxen.

Methods

The study included 53 children, aged between 3 months and 13 years. A dose of 10 mg/kg of oral naproxen suspension was administered.

A total of 270 blood samples (1-7 per patient) and 52 CSF samples (0-1 per patient) were obtained and measured by gas chromatography with mass spectrometric detection. Naproxen was measured as a total of bound and unbound drug. Additionally, from 52 of the blood samples, the concentration of unbound naproxen was measured (0-1 per patient). Modeling was done with NONMEM VI 2.0 and Perl-speaks-NONMEM [1].

Case deletion diagnostics (CDD) [1] were used to detect potential outliers. The following criteria were used for outlier identification: Covariance ratio less than 0.4 combined with Cook score above 1. Bootstrap was used to assess nonparametric confidence intervals for all parameters.

Results

In some individuals, the naproxen exposure was minimal. These individuals seemed to bias the pharmacokinetic parameter estimates. Two individuals fulfilled the CDD criteria for outlier identification. When these individuals were removed from the dataset, the standard errors of all parameter estimates decreased. Furthermore, the estimates of apparent volume of distribution and apparent clearance decreased.

The data were best described with a 2-compartment model. Absorption was modeled with simple first-order absorption with no lagtime.

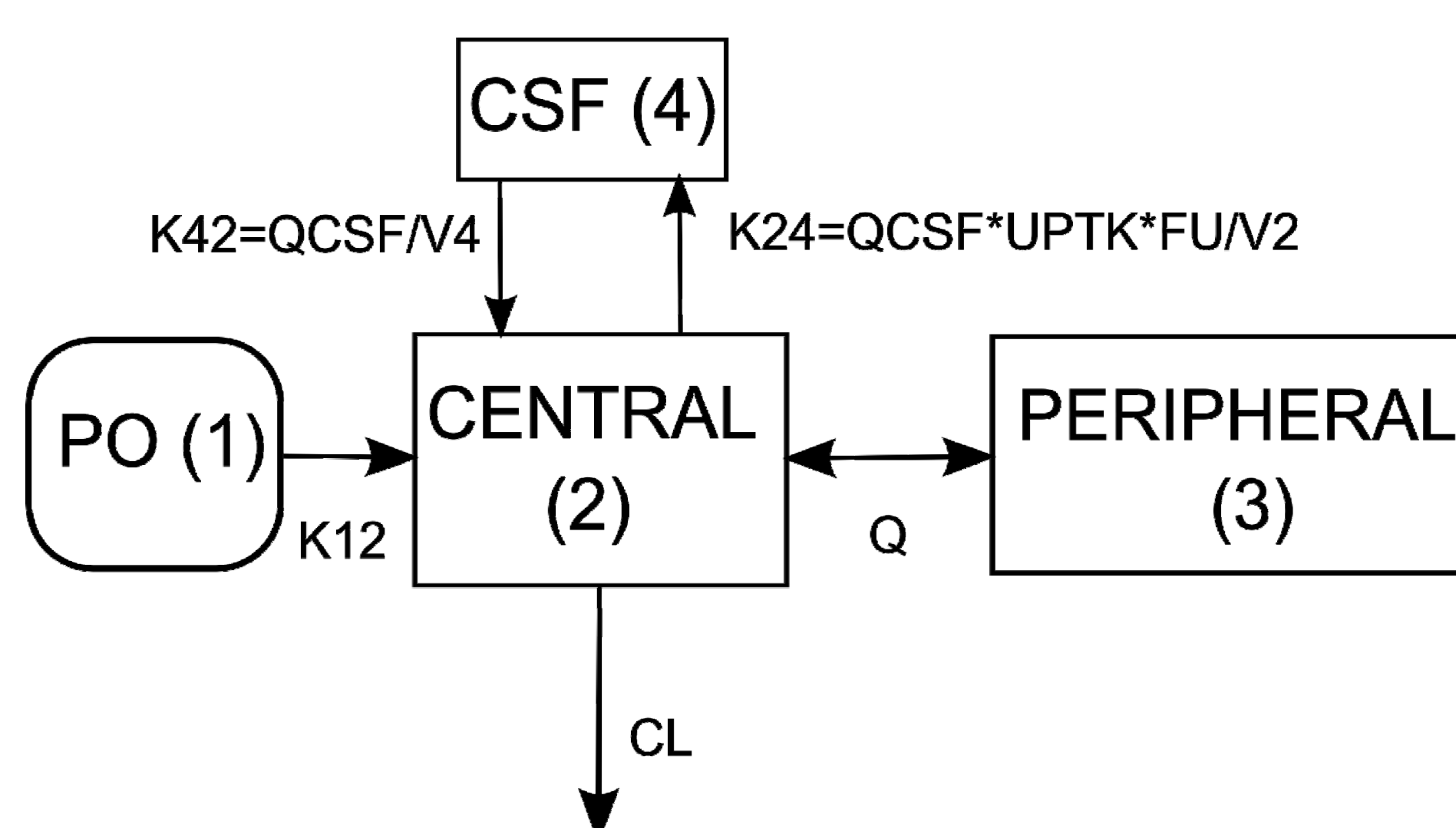


Figure 1: A diagram of the model

Apparent clearance was estimated to be $0.59 \text{ l h}^{-1} \cdot 70\text{kg}^{-1}$, and apparent volumes of distribution were estimated to be $7.4 \text{ l} \cdot 70\text{kg}^{-1}$ and $4.4 \text{ l} \cdot 70\text{kg}^{-1}$ for central and peripheral volume, respectively. The estimate of absorption rate constant was 1.1 h^{-1} .

The scaling of clearance with an exponent of 0.75 did not seem to improve the model. Furthermore, when the allometric exponent was estimated it became very close to 1 (estimate : 0.98 RSE: 10%) Thus, linear scaling by weight was used in the model. Figure 2 presents a Visual Predictive Check of the total plasma concentrations of naproxen after the exclusion of outliers that were identified by CDD.

On average, the concentrations of naproxen in CSF were about four times higher than the concentrations of unbound naproxen in plasma. The uptake factor (UPTK) parameter describes what would be the ratio of CSF naproxen concentration versus unbound plasma naproxen concentration at steady state. The estimate of UPTK was 7.8. The intercompartmental clearance between central compartment and peripheral compartment (QCSF) was 0.008 l h^{-1} according to the model. Figure 3 presents the raw concentration-time data of naproxen concentrations in the CSF in a semi-logarithmic plot.

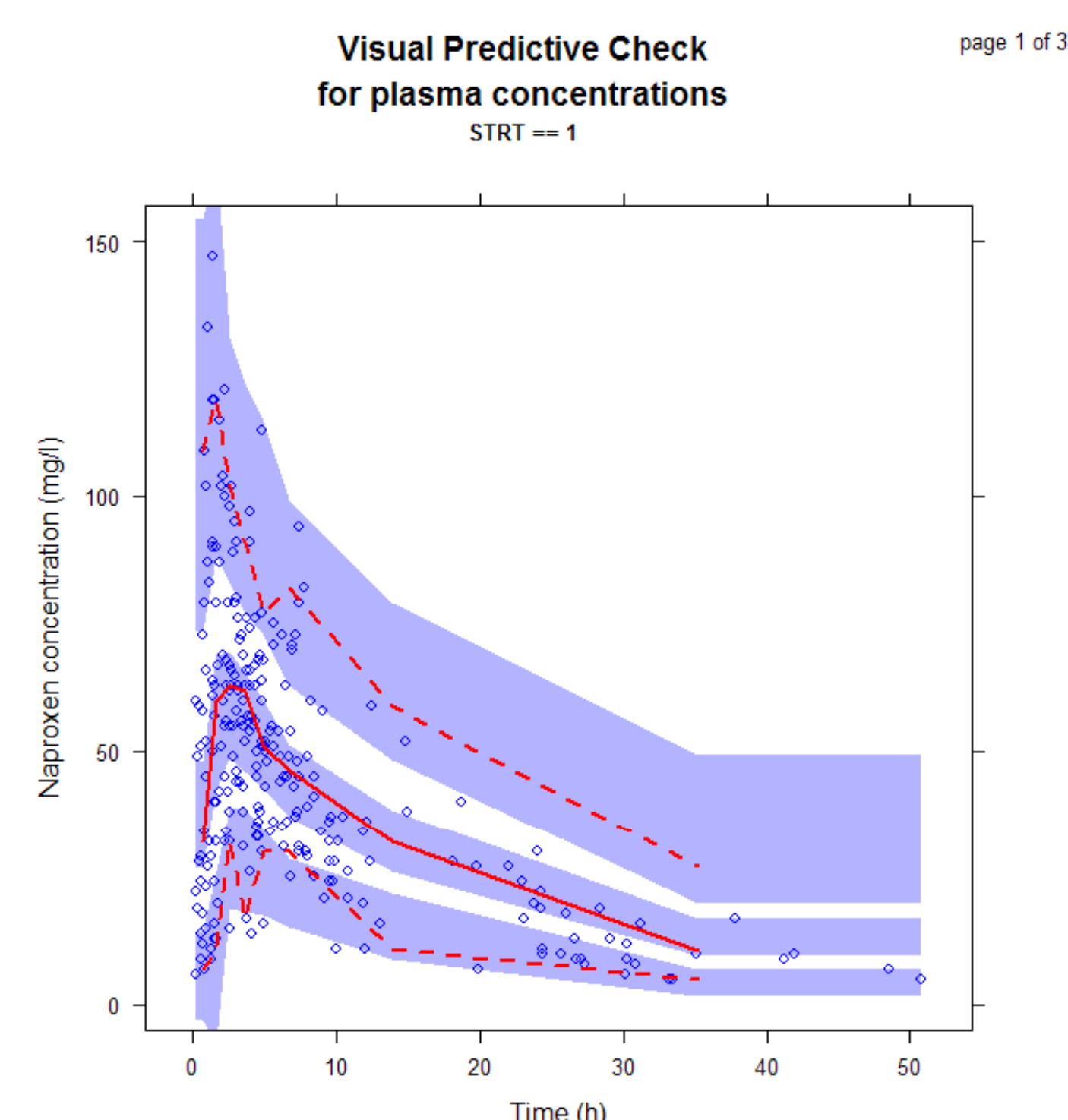


Figure 2: A Visual Predictive Check of plasma concentrations

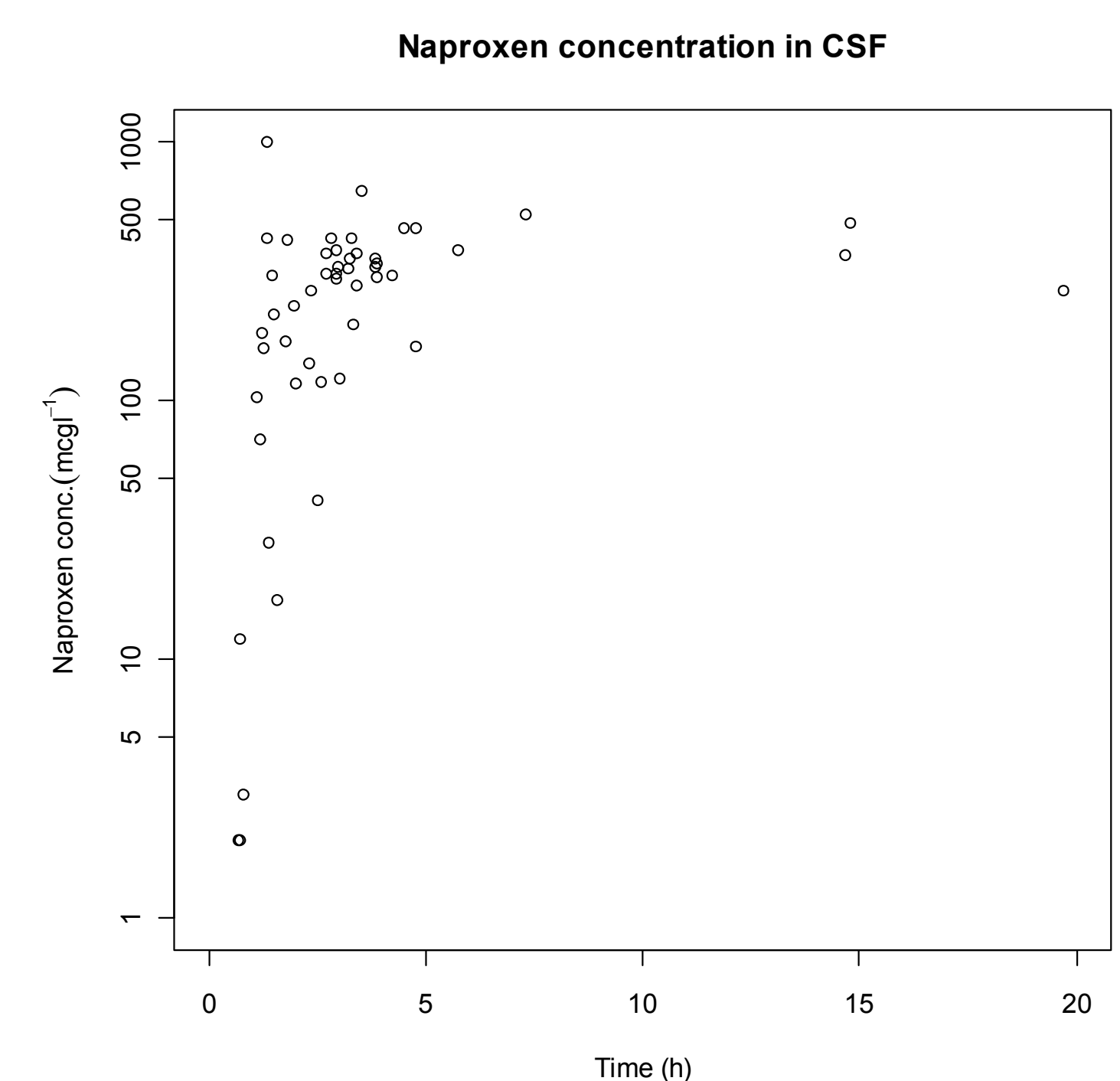


Figure 3: CSF concentrations of naproxen versus time

Conclusions

This is the first study on CSF distribution of naproxen in humans. This study is also first to address the pharmacokinetics of oral naproxen in children younger than 5 years old. Earlier studies have investigated the pharmacokinetics of naproxen in children aged 5-16 years [2,3]. The naproxen concentrations in CSF are higher than the concentrations of free naproxen in plasma. This is typical to lipophilic drugs with extensive protein binding[4].

References

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