

# PHARMACOKINETICS OF SUFENTANIL AFTER EPIDURAL AND INTRAVENOUS ADMINISTRATION IN CHILDREN AND INFANTS

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## OBJECTIVES

Sufentanil is a potent opioid widely used in anesthetic and intensive care management. Literature data describing pharmacokinetics of sufentanil in pediatric population are limited, while the clinical use of sufentanil increases in this population. The aim of this study was to develop a population model describing pharmacokinetics of sufentanil administered via intravenous and epidural infusion in children and infants.

## METHODS

Patients from two previous studies were included in the analysis: 41 children 0–18 years old receiving intravenous sufentanil infusion [1] and 20 infants 3–36 months old receiving epidural sufentanil infusion [2]. Population pharmacokinetic analysis was conducted using non-linear mixed effects modelling in NONMEM 7.3.0 software. Allometric scaling with theoretical exponents was implemented to account for changes in body size. Changes in metabolic clearance due to maturation of enzyme activity were characterized as a fraction of adult clearance by Hill equation. The relationships between covariates and the typical values of PK parameters are presented in Equation 1. Model selection was guided by the change in objective function value (OFV) and diagnostic plots, including visual predictive checks. Precision of parameter estimates was assessed by nonparametric bootstrap.

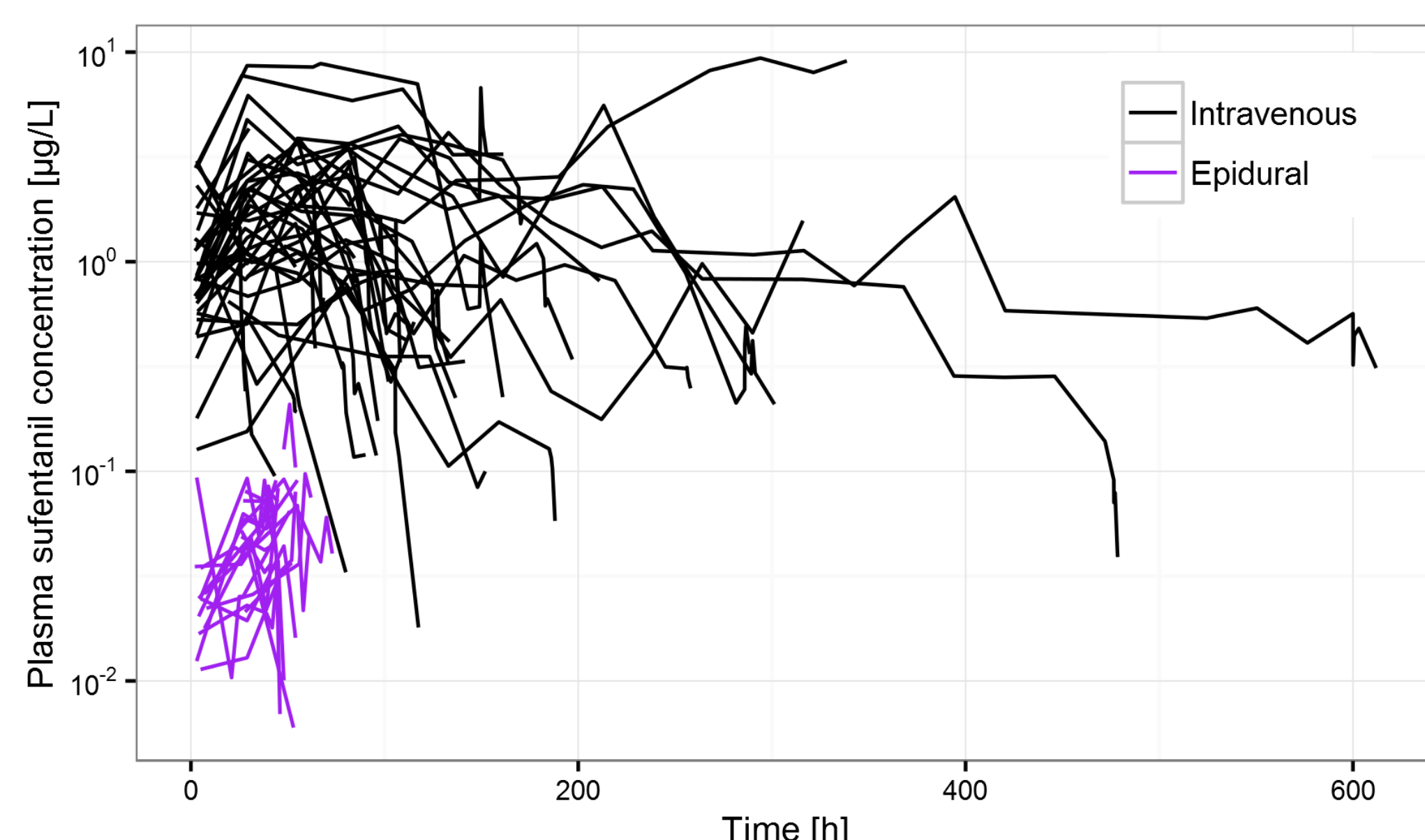


**Figure 1.** The individual sufentanil concentration-time profiles after intravenous (black lines) and epidural (purple lines) administration.

$$\begin{aligned} k_a &= \theta_{ka} \cdot e^{\eta_1} \\ V_c &= \theta_{vc} \cdot \frac{BW}{70} \cdot e^{\eta_2} \\ CL &= \theta_{cl} \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot \frac{PMA^{Hill}}{PMA^{Hill} + T_{50}^{Hill}} \cdot e^{\eta_3} \\ Q &= \theta_Q \cdot \left(\frac{BW}{70}\right)^{0.75} \cdot e^{\eta_4} \\ V_T &= \theta_{vt} \cdot \frac{BW}{70} \cdot e^{\eta_5} \end{aligned}$$

**Equation 1.** Relationships between covariates and typical PK parameters.

## RESULTS

A two-compartment model with first-order absorption sufficiently described sufentanil pharmacokinetics. Typical values of the central and peripheral volume of distribution, metabolic and inter-compartmental clearance for a theoretical patient of 70 kg weight were as follows:  $V_C = 7.85$  L,  $V_T = 475$  L,  $CL = 52.0$  L/hr, and  $Q = 40.5$  L/hr. The effect of body weight on disposition PK parameters was well accounted for by allometric scaling with theoretical exponents. The typical value of absorption rate constant from epidural space ( $k_a$ ) was  $0.047$  h<sup>-1</sup>. The values of Hill coefficient and postmenstrual age at which enzyme activity is 50% of the mature value were 2.80 and 33.6 weeks respectively. The inter-individual variability was estimated for  $k_a$ ,  $CL$ ,  $V_T$ , and  $Q$ .

| Parameter [unit]                   | Estimate | %CV  | Shrinkage | Bootstrap mean | Bootstrap 10th | Bootstrap 90th |
|------------------------------------|----------|------|-----------|----------------|----------------|----------------|
| $\theta_{ka}$ [1/h]                | 0.047    | 16.8 |           | 0.046          | 0.037          | 0.059          |
| $\theta_{vc}$ [L]                  | 7.85     | 41.1 |           | 7.62           | 4.25           | 56.2           |
| $\theta_{cl}$ [L/h]                | 52.0     | 9.8  |           | 53.0           | 46.3           | 198.1          |
| $\theta_Q$ [L/h]                   | 40.5     | 16.2 |           | 39.3           | 31.3           | 48.6           |
| $\theta_{vt}$ [L]                  | 475      | 21.4 |           | 466            | 360            | 607            |
| $\theta_{T50}$ [weeks]             | 33.6     | 21.6 |           | 38.4           | 28.3           | 1938           |
| $\theta_{Hill}$                    | 2.80     | 57.1 |           | 3.14           | 0.49           | 7.11           |
| <b>Between-subject variability</b> |          |      |           |                |                |                |
| $\omega^2_{ka}$                    | 42       | 63   | 68.2      | 38             | 1              | 56             |
| $\omega^2_{vc}$                    | 0 FIX    |      | 100       |                |                |                |
| $\omega^2_{cl}$                    | 48       | 22   | 8.6       | 47             | 40             | 54             |
| $\omega^2_Q$                       | 64       | 41   | 43.5      | 60             | 33             | 80             |
| $\omega^2_{vt}$                    | 110      | 32   | 29.8      | 109            | 82.3           | 137            |
| <b>Residual error model</b>        |          |      |           |                |                |                |
| $\sigma^2_{prop}$                  | 36.5     | 4.8  | 9.9       | 36.5           | 33.9           | 38.7           |

**Table 1.** The parameter estimates of the final PK model of sufentanil. The bootstrap (n=1000, failed=356) estimates are given for comparison.

**Figure 2.** Relationship of clearances (CL) and body weight normalized clearances (CL/BW) versus age for all patients in the study.

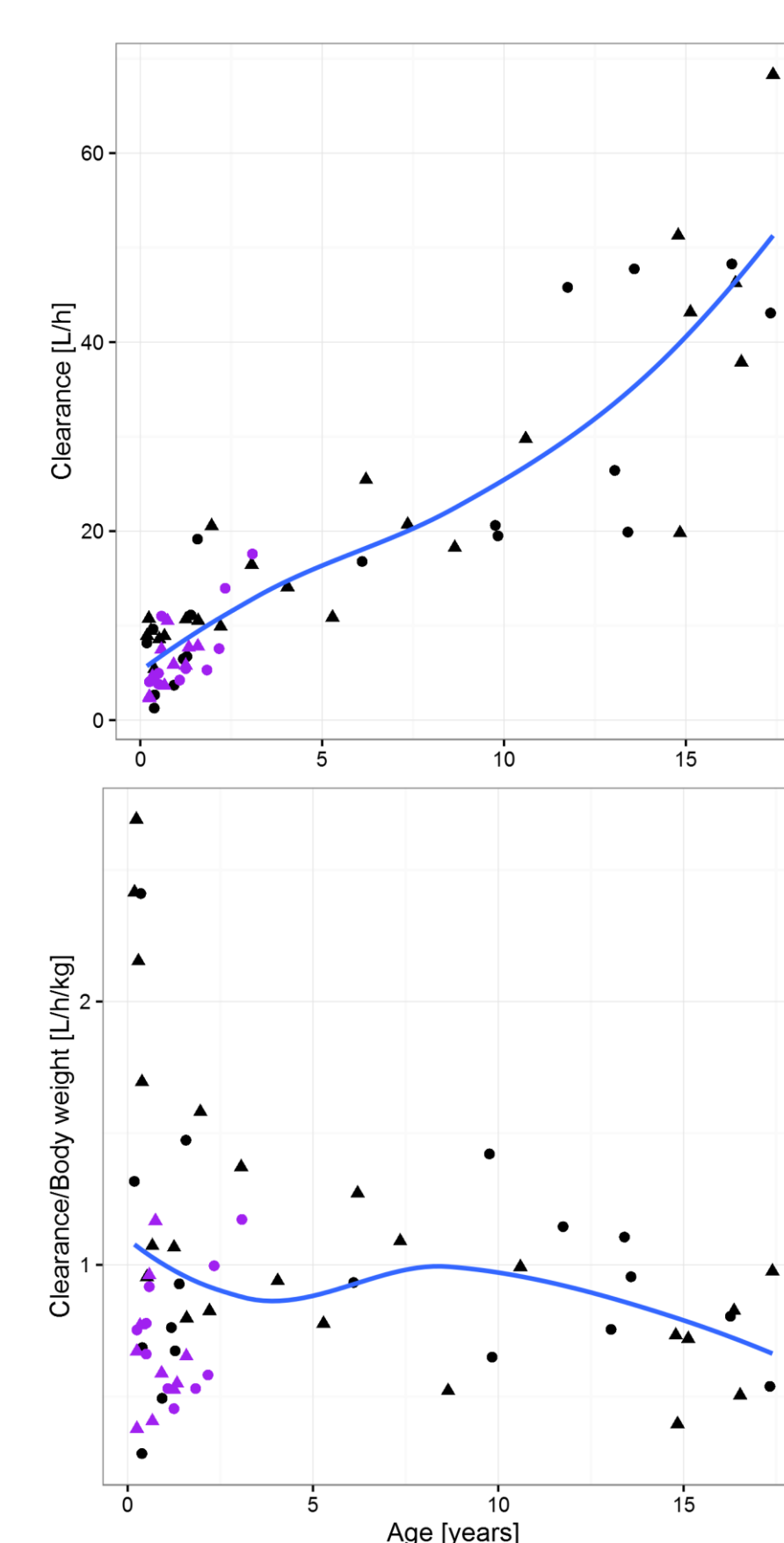


**Figure 3.** Correlation between ETAs and covariates.

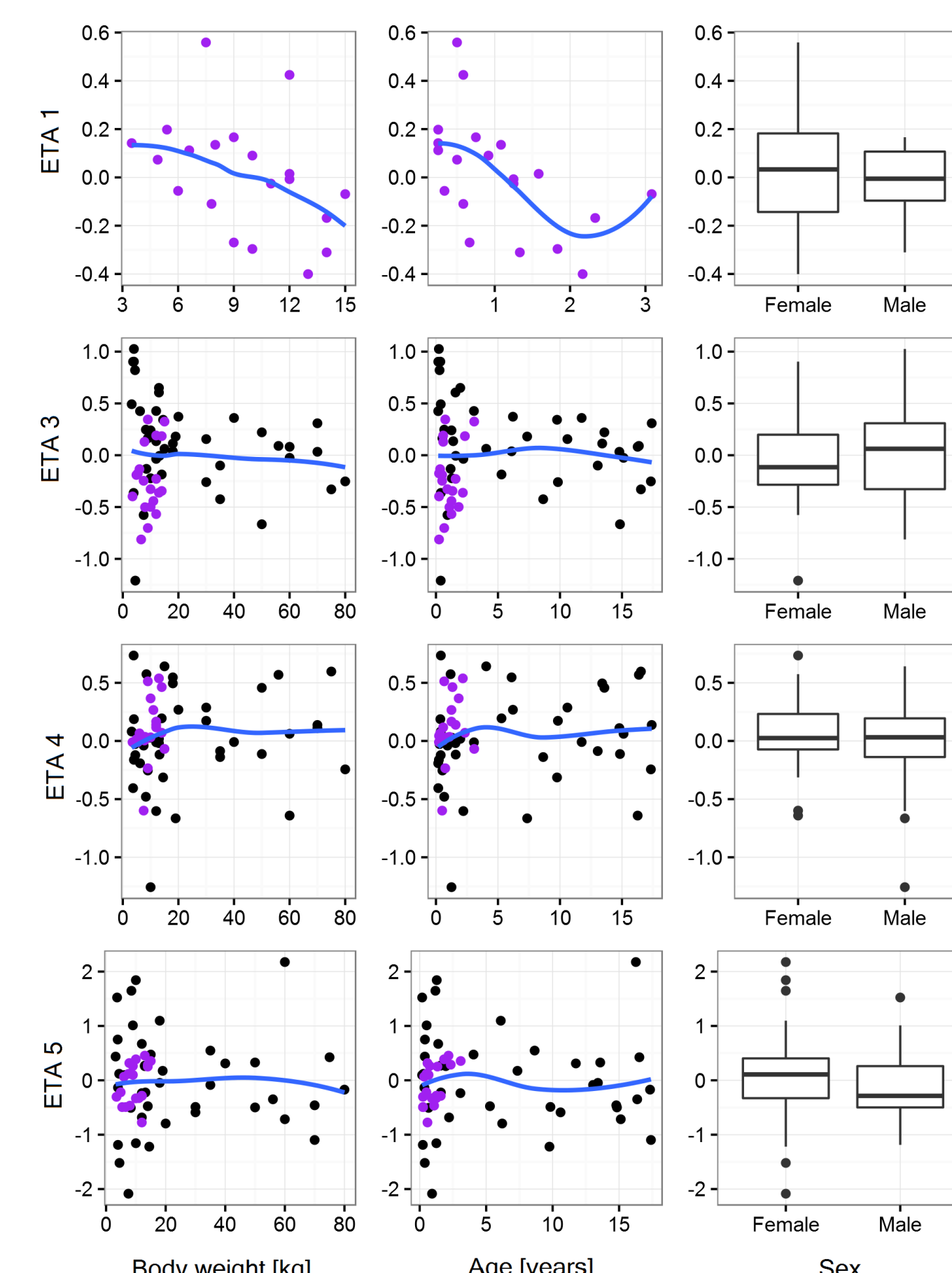


**Figure 4.** Goodness of fit plots: observed versus individual predicted concentrations; conditional weighted residuals (CWRES) versus time and CWRES versus individual predicted concentrations.

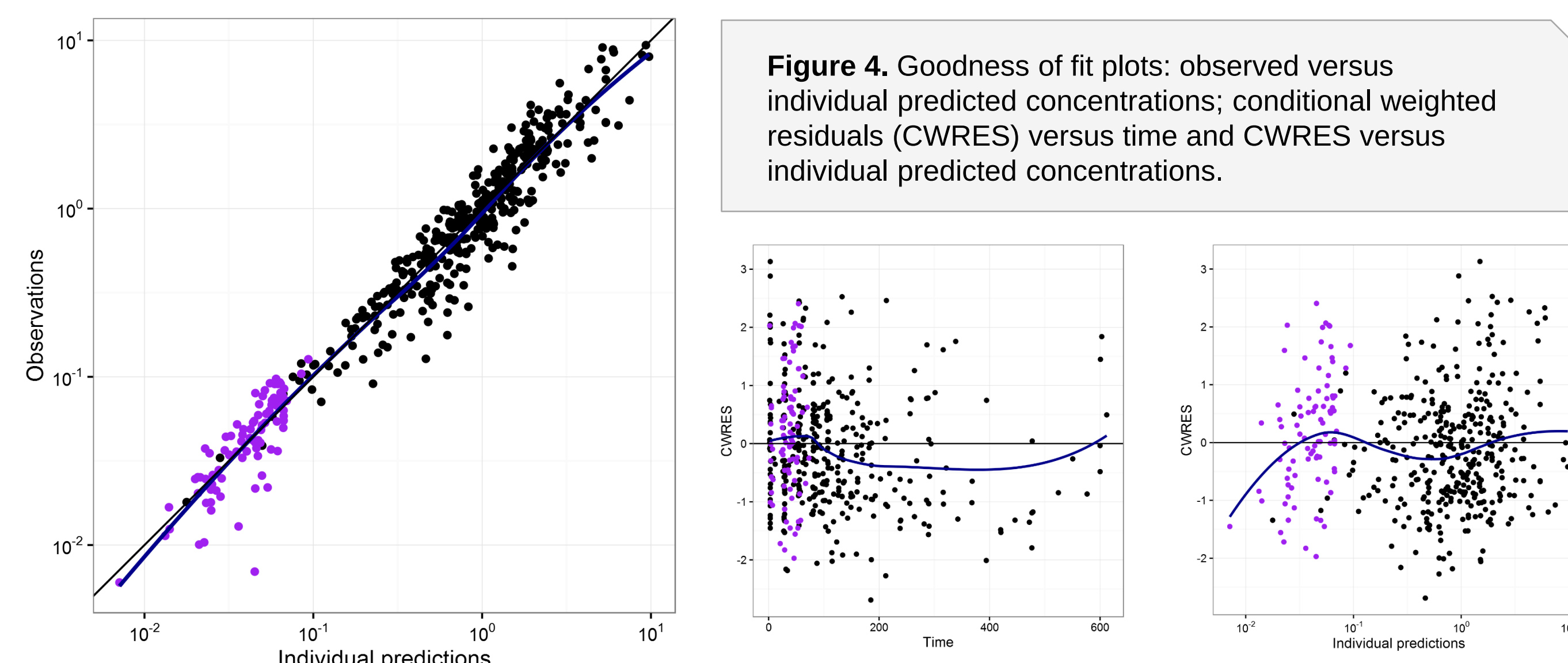


**Figure 5.** Prediction-corrected visual predictive check – subset of data during the time of sufentanil infusion.

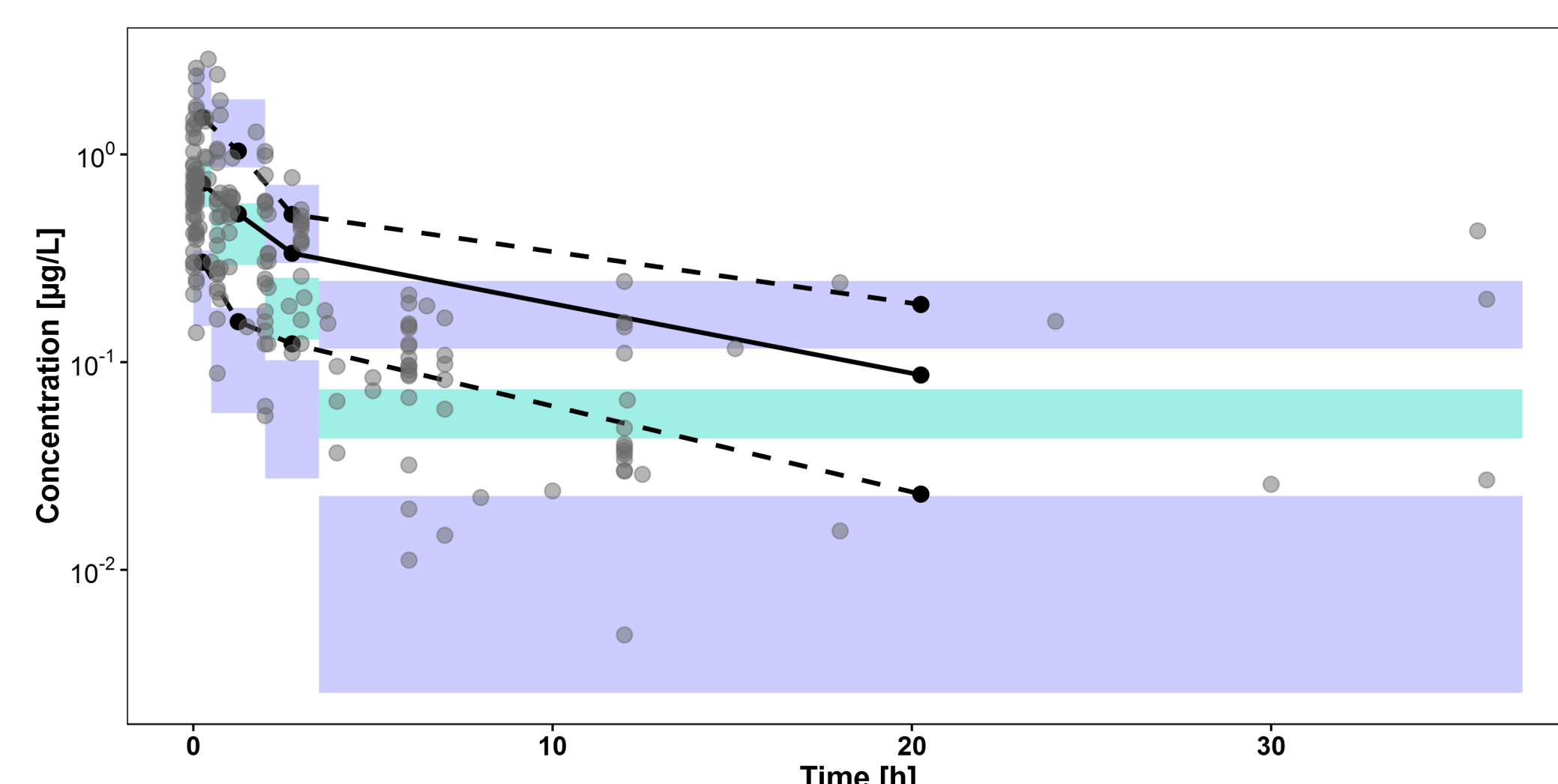
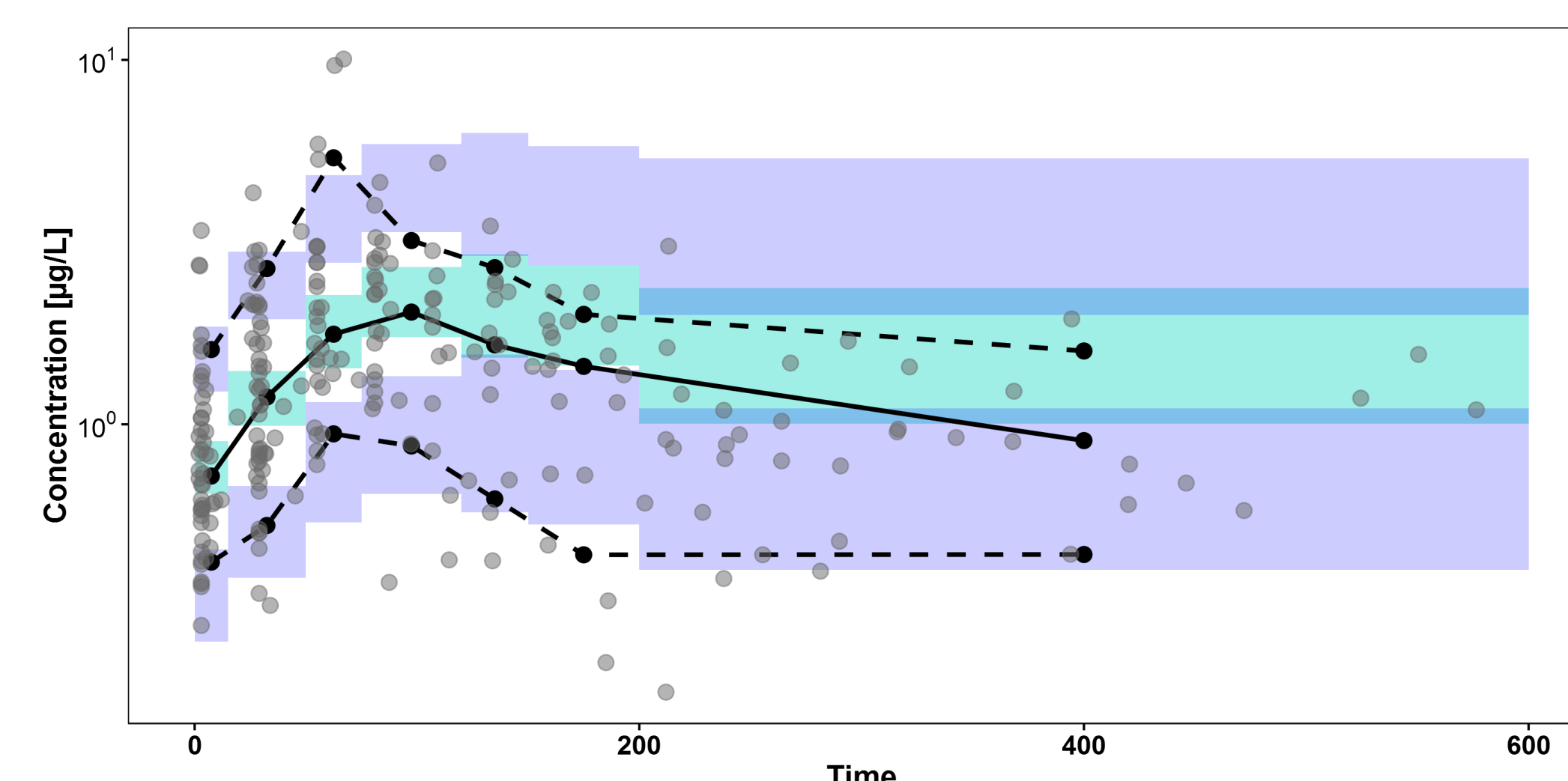


**Figure 6.** Prediction-corrected visual predictive check – subset of data after the end of sufentanil infusion.

## CONCLUSIONS

Population pharmacokinetic model was successfully developed to describe the time course and variability of sufentanil concentrations in children and infants. The model suggests slow absorption of sufentanil administered via epidural infusion. However, estimated absorption rate constant is based on sparse data. Future work will focus on including additional patients receiving sufentanil via epidural infusion with more dense sampling schedule.

## REFERENCES

- [1] Bartkowska-Śniatkowska A, Bienert A, Wiczling P, et al. Pharmacokinetics of sufentanil during long-term infusion in critically ill pediatric patients. J Clin Pharmacol 2016; 56: 109–15.
- [2] Wołoszczuk-Gębicka B, Grabowski T, Borucka B, Karas-Trzeciak M. Pharmacokinetics of sufentanil administered with 0.2% ropivacaine as a continuous epidural infusion for postoperative pain relief in infants. Paediatr Anaesth 2014; 24: 962–7.

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