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ORIGINAL RESEARCH

Population Pharmacokinetic of Epidural Sufentanil in Labouring Women: A Multicentric, Prospective, Observational Study

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Purpose: The effects of sufentanil-ropivacaine combination on the parturient women and the course of labor have been well documented. However, there is little information regarding the time-dependent pharmacokinetic characteristics of sufentanil after epidural administration in laboring women. We aimed to develop a population PK model for epidural sufentanil in laboring women to evaluate the sufentanil placental transfer quantitatively.

Patients and Methods: Forty-one participants who underwent epidural labor analgesia were recruited into this study. Patients received a continuous epidural infusion of sufentanil 0.3 μg/mL with ropivacaine 0.1%. Maternal venous blood samples and umbilical venous blood samples were collected for population PK analysis. The trends of sufentanil blood concentrations in the mothers and umbilical cord were predicted by the model.

Results: Sufentanil disposition after continuous epidural administration in laboring women followed a two-compartment pharmacokinetic model. The estimated sufentanil central clearance (CL), central volume of distribution (V1), clearance between central compartment and umbilical cord compartment (CL2), and umbilical cord volume of distribution (V2) were 176 L/h, 519 L, 0.0134 L/h, and 0.187 L. The absolute level of sufentanil in placental circulation is low after epidural administration. A slow decline in placental sufentanil concentration was predicted by the final PK model after epidural infusion was discontinued.

Conclusion: A slow decline in placental sufentanil concentration is predicted by the final two-compartment PK model after epidural infusion was discontinued. This suggests that very large doses of epidural sufentanil should be avoided during labor analgesia.

Trial Registration: https://www.chictr.org.cn, No: ChiCTR1800018810.

Keywords: pharmacokinetic, sufentanil, epidural, labour, pain

Introduction

Epidural analgesia is a very popular and effective technique to reduce labor pain.[1,2] A low concentration of local anesthetic combined with an opioid is the commonly used medication for this procedure. Sufentanil is a synthetic opioid drug, which has a rapid onset due to its high lipophilicity, and has been recommended as an adjuvant for epidural labor analgesia. The addition of sufentanil to local anesthetics has been shown to provide satisfactory labour analgesia and reduce the dosage of local anesthetics.[3–5] However, highly lipophilic agents have been theoretically considered to easily undergo placental and dural transfer. Placental transfer of sufentanil is a dynamic process with epidural continuous infusion. Therefore, the population PK model can provide a comprehensive overview of this process.

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Many physiological changes occur during pregnancy which may alter the pharmacokinetics (PK) of many drugs. Moreover, the presence of fetal and placental tissues provides another compartment where drugs are distributed. The effects of sufentanil-ropivacaine combination on the parturient women and the course of labor have been well documented.[6,7] However, there is little information regarding the time-dependent pharmacokinetic characteristics of sufentanil after epidural administration in laboring women. The population PK model could provide valuable information regarding maternal medication. In this prospective multicenter study, we aimed to develop a population PK model describing the pharmacokinetic of sufentanil co-administered with 0.1% ropivacaine as an epidural infusion in laboring women.

Materials and Methods

Subjects and Clinical Data Collection

The data used in this study were acquired during a previous clinical trial that investigated the analgesic effects of epidural infusion of nalbuphine and ropivacaine compared to sufentanil and ropivacaine (https://www.chictr.org.cn, ChiCTR1800018810).[8] The drug concentration measurements were conducted in February 2020, and data extraction began in March 2020. This study included in our previous study was approved by the Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University (No.: 2018–52; Chairperson Prof. Hua Jiang). Written informed consent was obtained from all participants. Between November 2018 and February 2019, women meeting the following criteria were enrolled in the study: American Society of Anesthesiologists (ASA) physical status II–III, 20–40 years, body mass index (BMI) of 18.5–30 kg/m^2, primiparas, singleton pregnancy and cervical dilation of $2 \leq \varphi < 6$ cm before analgesia. The exclusion criteria were as follows: (1) cardiopulmonary disease, diabetes requiring insulin treatment, and neuromuscular diseases, (2) alcohol and drug abuse, (3) allergy, (4) a visual analogue scale (VAS) score <50 mm before analgesia, and (5) contraindications of epidural anesthesia. Included parturients were excluded from subsequent analyses under the following conditions: (1) did not need patient-controlled analgesia (PCA), (2) VAS score did not decrease to 40 or less or more than 50% from the baseline value 30 minutes after drug administration and therefore required an additional 10 mL of 0.2% ropivacaine, and (3) epidural catheter became detached or displaced during continuous analgesia.

Anesthesia Management

When parturients wanted to have epidural analgesia, an intravenous 500 mL Ringer's solution was administered at a rate of 20 mL /min. After placing an indwelling epidural catheter as a routine procedure, the mother was given an epidural injection of 0.1% ropivacaine and 3μg/mL sufentanil mixture. The initial epidural dose consisted of 5 mL the mixture solution with 1/400,000 epinephrine. Five minutes later, a 10 mL bolus of the epidural medication was given. Thirty minutes later, the epidural catheter was connected to an electronic pump, and patient controlled epidural analgesia (PCEA) was initiated. The PCEA settings included the options for a bolus dose of 6 mL, locking interval of 15 minutes, continuous infusion rate of 6 mL/h and maximum hourly dose of 30 mL. The epidural infusion was maintained throughout the second stage of labor until delivery. If breakthrough pain occurred, it was treated with a 10 mL bolus of 0.2% ropivacaine. If the VAS score remained above 40mm, further pain management was at the discretion of the charge anesthesiologist.

Sample Collection and Plasma Concentration Assay

Maternal venous blood samples were taken at 0.5h and 1h after the epidural loading dose, at delivery, and 2h after delivery. Umbilical venous blood samples were also drawn immediately after clamping the umbilical cord to assess drug transfer. It was planned to collect samples at four time points for each patient. However, due to the difficulty of obtaining maternal blood samples during labour, not all four samples were mandatory. Nevertheless, it was encouraged to collect as many samples as possible for each patient. Each blood sample (4 mL) was collected in a heparin-containing tube as an anticoagulant. The samples were then centrifuged at 4000 rpm for 10 min at 4°C, and the plasma was promptly stored at −80 °C until analysis. The plasma concentration of sufentanil was determined using a validated LC-MS/MS system (Sciex Triple QuadTM6500+). The plasma samples were denatured with acetonitrile containing 200 ng/mL sufentanil-d 5 as an internal standard. The mixture was vortexed and centrifuged at 4000rpm for 5 min at 4 °C. For the HPLC analysis of sufentanil, an analytical

column (4.6 × 50 mm; particle size 3.5μm; Eclipse Plus, Agilent Technologies, CA, USA) was used with a mobile phase consisting of 1mmol/l ammonium acetate in acetonitrile at a flow rate of 0.8 mL/min. The lower limit of quantification was 1pg/mL of sufentanil. The inter- and intra-assay coefficients of variation were both less than 15%.

Sufentanil Structural Pharmacokinetic Model

The schematic representation of the model is shown in Figure 1 and the corresponding different equations are provided below. In this model, the drug is administered to the epidural compartment and then distributed to the central compartment. However, due to limited data, the parameters of the epidural compartment could not be estimated accurately. Therefore, for the purpose of this analysis, it was assumed that the epidural compartment merged with the central compartment. The pharmacokinetic model of sufentanil was developed based on the concentrations observed in the central compartment (compartment 1) and the umbilical cord compartment (compartment 2) simultaneously. In the equations, A1 and A2 represent the amount of drug in the central compartment and umbilical cord compartment, respectively. V1 and V2 represent the volume distribution of the central compartment and umbilical cord, respectively. K_{12} and K_{21} are the rate constants governing the transfer between compartment 1 and compartment 2 (K_{12} = CL2/V1, K_{21} = CL2/V2). K_{10} represents the elimination rate constant from the central compartment (K_{10} = CL/V1).

$$\frac{dA1}{dt} = k21 \cdot A(2) - (k10 + k12) \cdot A \tag{1}$$

$$\frac{dA2}{dt} = k12 \cdot A(1) - k21 \cdot A \tag{2}$$

In this study, sufentanil blood concentrations in the mothers and umbilical cord were also predicted by the model so as to describe the placental transfer quantitatively. The model was parameterized in terms of central clearance (CL), central volume of distribution (V1), umbilical cord volume of distribution (V2), and clearance between central compartment and umbilical cord compartment (CL2).

Population PK Model Development

The population PK model for sufentanil was developed using the first-order conditional estimation method with interaction (FOCE+I) algorithm in the nonlinear mixed effects modelling software. Model visualization and evaluation were performed using the estimated parameters. Based on the goodness-of-fit assessment, a two-compartment model provided a better fit to the data compared to than one- or three-compartment pharmacokinetic models. Inter-individual variability (IIV) for the PK parameters was assumed to follow a log-normal distribution, modeled using an exponential relationship with the random effect η_i as follow:

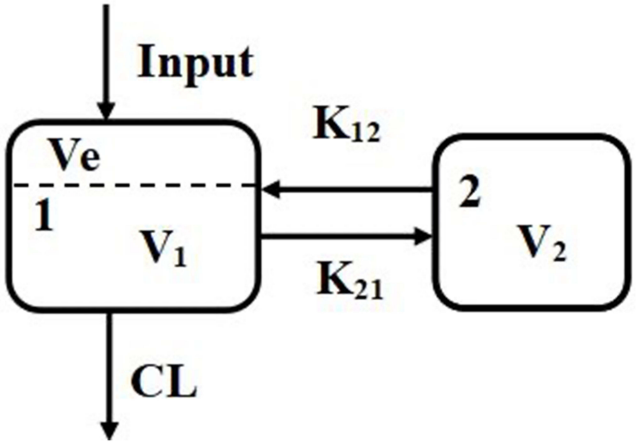

Figure 1 Schematic representation of the sufentanil pharmacokinetic model. V_e, epidural compartment; V_1, central compartment; V_2, funicle umbilical cord compartment. K_{12} and K_{21} are the rate between central and umbilical cord compartment.

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$$P_i = P_{TV} \times exp(\eta_i) \tag{3}$$

In the equation, P_i represents the individual value of the parameter P in the ith individual, P_{TV} is the population value of the parameter, and $\eta_i$is a random variable with a mean of zero and a variance of $\omega\eta^2$.

The intra-individual variability of concentrations in the central compartment and umbilical cord compartment was modeled using a proportional combined additive residual variability, as shown in the below formula:

$$C_{\text{obs}} = C_{\text{pred}} * \left(1 + \varepsilon_{\text{prop}}\right) + \varepsilon_{\text{add}} \tag{4}$$

where C_{pred} is the predicted concentration, C_{obs} is the observed concentration, ε_{prop} and ε_{add} are random numbers draw from normal distributions with a mean of zero and variance of $\sigma_1{}^2$ and $\sigma_2{}^2$, respectively. During the model process, ε_{add} was removed due to its less er significance.

The model`s bias was assessed using various goodness-of-fit plots (observed versus population predicted concentrations, observed versus individual predicted concentrations, conditional weighted residuals [CWRES] versus population predicted concentrations, and CWRES versus time after dosing). Additionally, individual plots were visually inspected for improvements, and confidence intervals of parameter estimates and shrinkage were considered.

Model Evaluation and Simulations

To evaluate the stability of the final model, a non-parametric bootstrap analysis was performed using the PsN Toolkit. A bootstrap analysis with 5000 runs was conducted using the final model to assess the internal validity of the parameter estimates and their corresponding 95% confidence intervals (CIs). The model's performance was further evaluated using prediction-corrected visual predictive checks (pc-VPCs). One thousand datasets were simulated from the final model, and the median and 95% CI of the simulated data were plotted alongside the observed concentrations.

Data Analysis

The population PK model for sufentanil was developed with a non-linear mixed-effects modeling software (NONMEM, version 7.4.0; ICON Development Solutions, Ellicott City, MD, United States) compiled with GFortran (version 4.6.0, https://gcc.gnu.org/fortran) and interfaced with Perl speaks-NONMEM (version 3.6.4; https://uupharmacometrics.github.io/PsN). The organization of raw data and the NONMEM output were performed with the R software (version 3.6.4; https://www.r-project.org).

Results

Patient Characteristics

Between November 2018 and February 2019, 90 parturients were recruited for sufentanil epidural labor analgesia. Eventually, 41 women, 27.2 ± 2.9 years old, and weight 70.2 ± 7.5 kg, were enrolled in the final population PK analysis. The sufentanil PK analysis included 79 and 37 concentration samples from the central compartment and umbilical compartment, respectively. The total number of samples varied due to inadequate blood volume or inability to obtain blood at some sampling time points. Some planned sampling times were slightly deviated, but the actual sampling times were recorded and used in the pharmacokinetic calculations. These deviations were unlikely to have affected the results.

Plasma Concentrations of Sufentanil

The Plasma concentrations of sufentanil versus time profiles for the central compartment (left) and umbilical cord (right) are shown in Figure 2.

Population Pharmacokinetic Modeling

The results of parameter estimates and their inter-individual variation (IIV) are summarized in Table 1. The estimated sufentanil CL, V1, CL2 and V2 were 176 L/h, 519 L, 0.0134 L/h, and 0.187 L, respectively. The addition of IIV to CL2 and V2 did not contribute to better model fitting and was therefore not included in the final estimates.

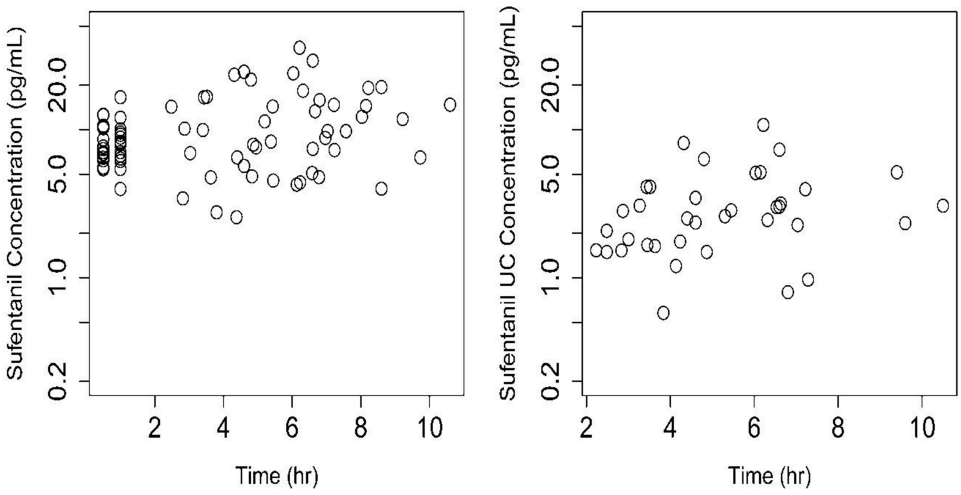

Figure 2 Plasma concentration of sufentanil versus time profile for central compartment (left) and umbilical cord compartment (right).

Model Evaluation and Simulation

The goodness-of-fit plots suggested a favorable fit for sufentanil pharmacokinetic model (Figure 3). The observed concentration and the population-predicted concentration from the central compartment as well as the umbilical cord were distributed evenly around identity line, as was the observed concentration versus the individual-predicted concentration (Figure 3 top). The changes in conditional weighted residual value (CWRES) over population-predicted concentrations were distributed evenly around 0, and most points were located within - 4 and 4 (Figure 3 bottom), illustrating the adequate model fit of the final models.

The individual fit plots for the final sufentanil pharmacokinetic model are presented in Figure 4. Maternal blood concentrations of sufentanil rapidly decreased once the epidural infusion was discontinued. However, the umbilical concentration of sufentanil remained unchanged or even slightly elevated immediately after delivery. Although the substantial placental transfer of sufentanil after epidural administration occurred, absolute level of sufentanil was extremely low.

Table 1 Population Parameter Estimates for the Final Sufentanil Pharmacokinetic Model

Parameter	Sufentanil Model Estimates (CV%)
Structural parameters	
CL (L/h)	176 (9.25%)
V1 (L)	519 (6.45%)
CL2 (L/h)	0.0134 (43.2%)
V2 (L)	0.187 (39.9%)
Inter-individual variability	
IIV of CL	53.9 (12%)
IIV of V1	21.8 (26.9%)
Residual variability	
ε_{prop1} (%)	20.6 (13.4%)
ε_{prop2} (%)	35.5 (12%)

Abbreviations: CL, central clearance; V1, central volume of distribution; V2, umbilical cord volume of distribution; CL2, clearance between central compartment and umbilical cord compartment; IIV, inter-individual variability; ε_{prop1}, proportional residual variability of central compartment, respectively; ε_{prop2}, proportional residual variability of umbilical cord compartment, respectively.

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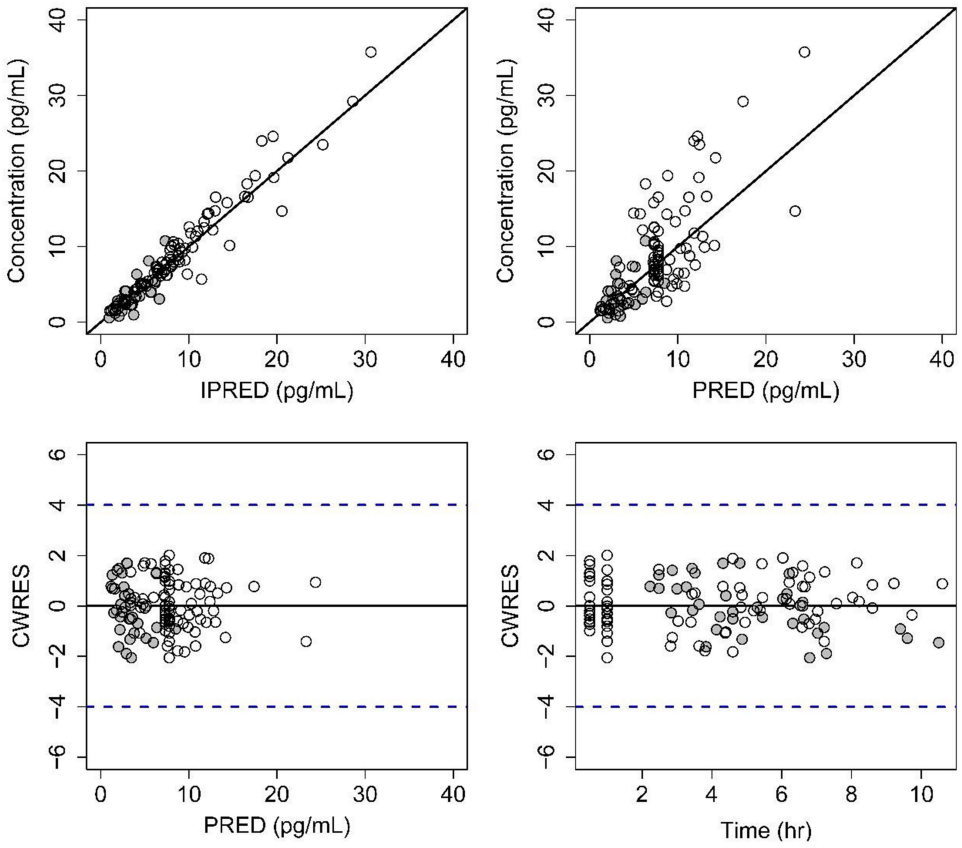

Figure 3 Goodness-of-fit plots for the final sufentanil pharmacokinetic model. Illustrating population predictions versus observed concentrations, individual predictions versus observed concentrations, conditional weighted residuals(CWRES) versus time, conditional weighted residuals (CWRES) versus population prediction. The fine line is the line of identity. The open circles and solid gray dots are plasma concentrations from central compartment and umbilical cord compartment, respectively.

However, predicted by the final population pharmacokinetic model, the concentration in the placental circulation still maintained a relative high level and decreased slowly even though epidural administration was discontinued.

The prediction corrected visual predictive checks (pc-VPCs) for the sufentanil (Figure 5) pharmacokinetic model revealed that the 5th to 95th percentiles of the predicted data overlaid most of the observed data, indicating good precision of the PK model.

Discussion

This study represents the first report on a population pharmacokinetic (PK) model of sufentanil administered epidurally in laboring women. Our results indicate that a two-compartment model with proportional error for inter-individual variability best fits the concentration data. In our final model, the typical maternal clearance for sufentanil after epidural administration was estimated to be 176 L/h. The typical maternal volumes of distribution were 519L for sufentanil. The clearances between the maternal compartment and umbilical cord compartment were 0.0134 L/h for sufentanil. Predicted by the final population pharmacokinetic model, the placental sufentanil concentration declines slowly after epidural infusion is ceased.

The maternal pharmacokinetic model developed in this study accurately and precisely predicted sufentanil plasma concentrations, as demonstrated by the results of the prediction-corrected visual predictive check plots. Bootstrap analysis validation further confirmed the reliability and robustness of the parameter estimates and the population pharmacokinetic model. Our sufentanil assay had the greater degree of sensitivity lower limit on the detection of 1pg/mL compared with 0.01–0.05ng/mL in other studies.[9,10] Based on the accurately measured concentration, our predicted model was supposed to be much more robust and precise.

Many studies have focused on placental transfer and metabolism by measuring drug concentrations in umbilical vessels and maternal veins at delivery and calculating fetomaternal (F/M) ratios. The placental transfer of sufentanil was

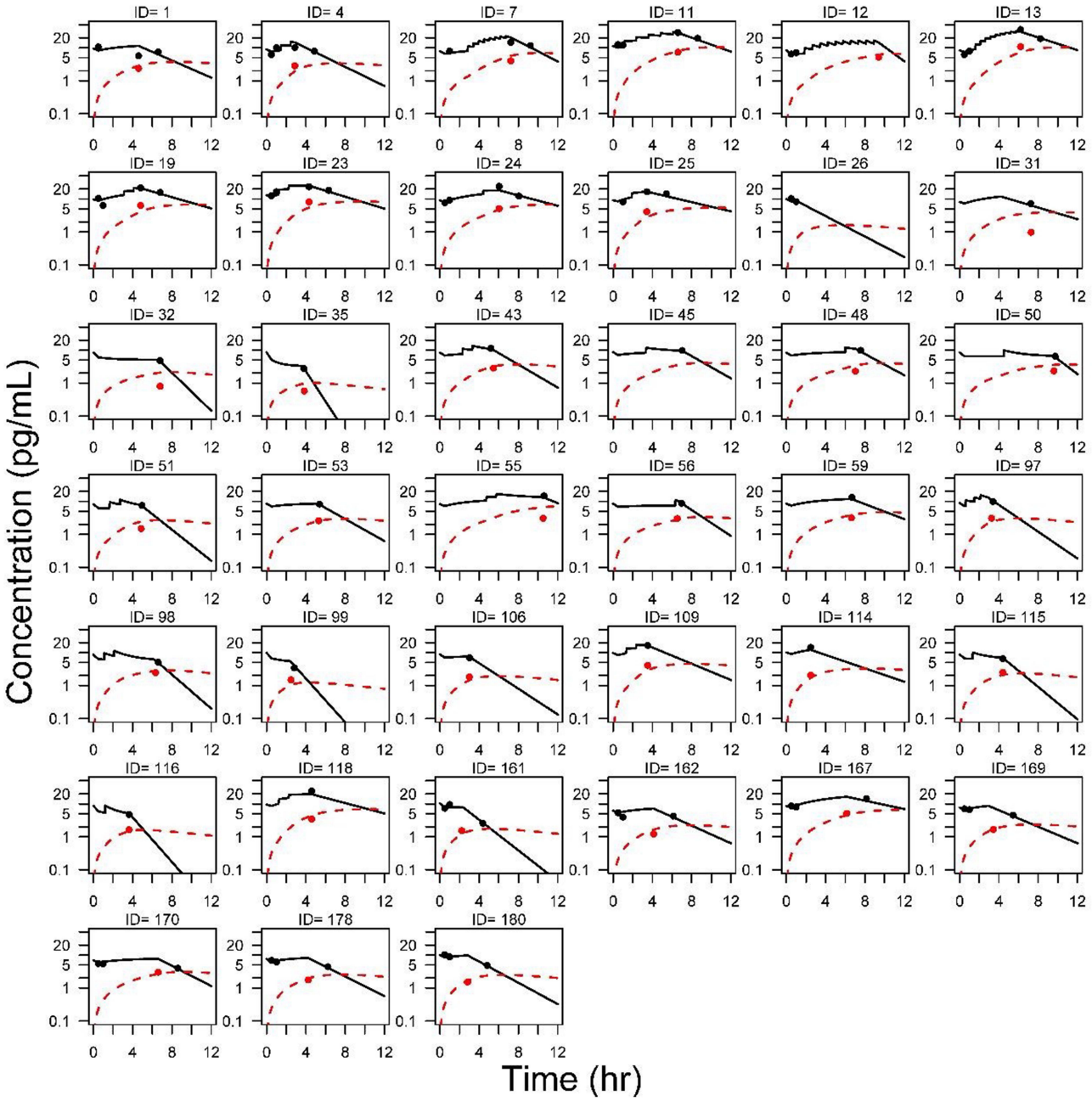

Figure 4 Individual fit plots for the final sufentanil pharmacokinetic model. The solid black lines and red dashed lines are the individual predictions of concentration by the final population pharmacokinetic model from central compartment and umbilical cord compartment, respectively. The black and red solid dots are the observed concentration from central compartment (n=40) and umbilical cord compartment (n=35) at delivery, respectively. The concentration-time profiles of five subjects without umbilical cord measurement were predicted by population mean PK parameters.

reported for 0.81 after epidural administration during labor in a previous study.[10] However, the interpretation of F/M ratios can be challenging due to the variability and non-comparability of results across different studies, particularly for drugs administered during delivery. Additionally, the F/M ratio reflects only the relative concentrations of the drug in the blood at one point in time (delivery), which may not provide a complete picture of the total amount of the drug. The timing of sampling relative to drug infusion by the mother can also impact the ratio. Moreover, the equilibrium across the placenta is established based on free drug concentrations, making F/M ratios less informative. In contrast, our study employed a population approach that maximized the information from limited data to study the placental transfer of drugs. By developing a population PK model, we were able to estimate the transfer rate of sufentanil from the mother to

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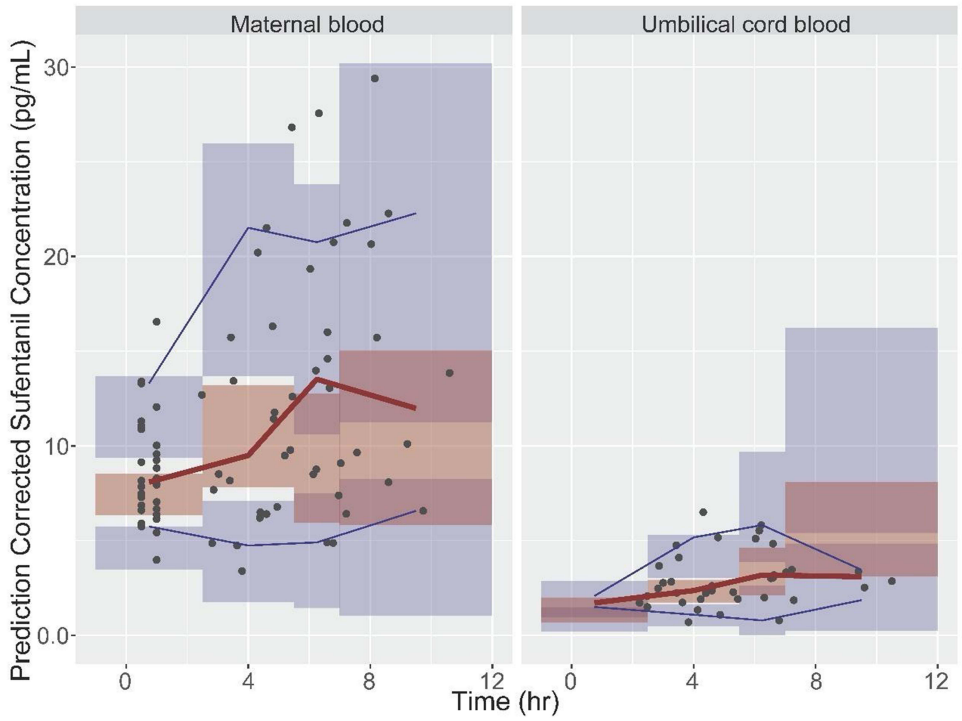

Figure 5 The prediction corrected visual predictive checks for the sufentanil pharmacokinetic model. T Sold circles represent observed concentration, and the red thick solid and thin blue lines represent median and the 95% CI of observation. The middle red shadow areas represent the 95% CI of the median for the results of 1000 times simulation of the model. The blue shadow areas represent the 95% CI of the 2.5th and 97.5th percentiles of the results of 1000 times simulation of the pharmacokinetic model.

the fetus. Our findings revealed that sufentanil disposition after continuous epidural administration in laboring women followed a two-compartment pharmacokinetic model. The distribution volume of sufentanil in the umbilical cord compartment was 0.19 L, which is almost negligible compared to 519 L in the central compartment. The transfer rate of sufentanil from the maternal blood to the umbilical blood was approximately 0.013 L/h. The speed was extremely slow. In view of the placental transfer rate of sufentanil, it is conceivable that the extent of fetal exposure to sufentanil was supposed to be low even though mothers received a long-term continuous epidural infusion.

Passive diffusion is the predominant route by which many drugs cross the placenta. It is generally considered that the drugs with high lipid solubility can easily cross the placenta. The octanol buffer distribution coefficients of sufentanil are 1737 which means its high lipophilicity.[11] Protein binding also influences the placental transfer of drugs, as only the unbound form of drugs is free to cross the placenta. Sufentanil has a high protein-binding ratio 93% which also contributes to the low degree of placental transfer. All the above factors could only partly affect placental transfer of sufentanil. However, the low degree of placental transfer mainly due to maternal low drug concentration and volume of distribution increased by pregnancy.

Individual fit plots for the final pharmacokinetic model in our study demonstrated that maternal blood concentrations of sufentanil rapidly decreased once epidural infusion ceased. However, the concentration of sufentanil in the umbilical cord compartment exhibited a more slow decay after epidural infusion was discontinued. In other words, predicted by the final population pharmacokinetic model in our study, fetus would be exposed to a relative high level of concentration even though stopping dosing sufentanil. Sufentanil could be likely sequestered in large amounts within the placenta as a result of its high lipophilicity and then released slowly into the placental circulation. Though clinically significant concentrations of sufentanil in the umbilical compartment have not been presented, sufentanil maybe potential affect the neonatal brain. A recent study has shown that fentanyl may cause autism-like behavioral changes in young mice.[12] Some other studies also reported that fentanyl may induce neurotoxicity, including impaired somatosensory, behavioural, cognitive, and motor functions during prenatal and perinatal periods.[13,14] The current clinical practice of epidural labor analgesia is that by increasing the concentration of

fentanyl or sufentanil, the local anesthetic concentration could be reduced to ensure the analgesic effect while reducing the incidence of motor block.[15,16] However, considering the slow decline in placental sufentanil concentration, it is advisable to avoid using very large doses of sufentanil in labor analgesia.

As a clinical study, there are some limitations in this study. First, although the observed concentrations were obtained from six research centers, the dataset was still relatively small, especially with only one umbilical blood sample for each patient. This might lead to inaccurate estimation of model parameters. A denser sampling design could have provided more robust predictive performance for the population PK model. However, obtaining umbilical cord blood samples before delivery is not feasible in clinical practice. Second, the parameters from this population pharmacokinetic model may not fully capture the pharmacokinetic behavior of sufentanil following continuous epidural administration due to the concomitant use of ropivacaine by the patients in this study. The potential risk of pharmacokinetic interactions should be considered. However, in clinical practice, it is routine to co-administer local anesthetics with opioid analgesics for labor analgesia. Therefore, the results from this study are more applicable to real-world clinical scenarios. Lastly, it should be noted that the interpretation of our results should consider the fact that the PK models developed in this study may not apply to all obstetric populations, as the placental barrier could be impaired by pregnancy-related diseases such as pre-eclampsia, eclampsia, gestational diabetes mellitus, and others.

To the best of our knowledge, this is the first published study on the population PK model of epidural sufentanil in laboring women. Our findings demonstrated that placental circulation accounts for only a small part of the large volume of sufentanil distribution and the maternal blood concentration is very low. Therefore, the absolute level of placental circulation appears to be extreme low although the substantial placental transfer of sufentanil after epidural administration occurs. However, a slow decline in placental sufentanil concentration was predicted by our PK model after epidural infusion ceased. For decreasing the extent of neonatal drug exposure, very large dose of sufentanil should be avoided during labor analgesia.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding authors.

Ethics Statement

This clinical trial was approved by the Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University (No.: 2018-52; Chairperson Prof. Hua Jiang) and conducted according to the International Conference on Harmonization–Good Clinical Practice Guidelines and the Declaration of Helsinki. The study was registered in the Chinese Clinical Trial Registry (https://www.chictr.org.cn, No: ChiCTR1800018810). All participated subjects provided written informed consent before this clinical trial initiation.

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Disclosure

The authors have no conflicts of interest to declare.

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