Sufentanil Disposition and Pharmacokinetic Model-Based Dosage Regimen for Sufentanil in Ventilated Full-Term Neonates

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Keywords

Neonate · Sufentanil · Pharmacokinetics · Dosage regimen · Critical care

Abstract

Introduction: Sufentanil is a potent synthetic opioid used for analgesia in neonates; however, data concerning drug disposition of sufentanil and dosage regimen are sparse in this population. Therefore, the aim of the study was to explore sufentanil disposition and to propose optimal loading and maintenance doses of sufentanil in ventilated full-term neonates. **Methods:** Individual sufentanil pharmacokinetic parameters were calculated based on therapeutic drug monitoring data using a 2-compartmental model. Linear regression models were used to explore the covariates. **Results:** The median (IQR) central volume of distribution (V_{d_c}) and clearance (CL) for sufentanil were 4.7 (4.1–5.4) L/kg and 0.651 (0.433–0.751) L/h/kg, respectively. Linear regression models showed relationship between V_{d_c} (L) and GA ($r^2 = 0.3436$; $p = 0.0452$) as well as BW ($r^2 = 0.4019$; $p = 0.0268$). Median optimal sufentanil LD and MD were 2.13 (95% CI: 1.78–2.48) $\mu\text{g/kg}$ and 0.29 (95% CI: 0.22–0.37) $\mu\text{g/kg/h}$, respectively. Median daily COMFORT-B (IQR) scores ranged from 6 to 23

while no significant relationship between pharmacokinetic parameters and COMFORT-B scores was found. **Discussion/Conclusion:** Body weight and gestational age were found as weak covariates for sufentanil distribution, and the dosage regimen was developed for a prospective trial.

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Introduction

Sufentanil is a potent synthetic opioid used for the analgesia approach in neonates and critically ill paediatric patients; however, data concerning drug disposition of sufentanil and dosage regimen are sparse in this population [1–5]. Sufentanil is metabolized via hepatic cytochrome P450 CYP3A4 by oxidative N-dealkylation into inactive metabolites and to a small extent excreted unchanged via the kidney (2%). However, the maturation of CYP3A4 is not fully understood while the CYP3A4-dependent drug clearance normalized per kg of body weight is significantly reduced in neonates, and it may increase over the first month or later during the postnatal life [6, 7]. CYP3A4 appears to be expressed in the foetal liver [8]. Pharmacokinetic (PK) data on sufentanil published in

critically ill neonates historically described volume of distribution (Vd) of 4.15 (1.01) L/kg, clearance (CL) 6.7 (6.1) mL/min/kg, and half-time of elimination ($t_{1/2}$) 737 (346) min [4]. A population PK model of sufentanil showed Vd of 6.87 L/kg and CL of 10.8 mL/min/kg in critically ill paediatric patients [9]. Furthermore, recently published data concluded that maturation, inflammation, and organ failure may have impact on the cytochrome P450 (CYP3A4)-mediated clearance of midazolam [10, 11]. There are very limited experimental and clinical PK data of sufentanil in critically ill neonates and young infants available in the literature [12, 13]. Therefore, we aimed to explore individual sufentanil PK parameters and its main covariates in order to propose, based on regression models, the optimal loading dose (LD) and maintenance dose (MD) of sufentanil in ventilated full-term neonates.

Materials and Methods

Study Population

An open-label retrospective observational study was performed in ventilated full-term neonates treated with sufentanil admitted to the Neonatal and Pediatric Intensive Care Unit of the Department of Pediatrics General University Hospital, First Faculty of Medicine Charles University in Prague from January 2014 to December 2015. At admission to the hospital, the patients' parents signed an approved general informed consent wherein they state, inter alia, that anonymous data can be used for research. The study-specific approval was issued by the local ethics committee under the No. 2219/20 S-IV. Our study follows the principles of the Declaration of Helsinki. Exclusion criteria were refusal of general informed consent.

Data Retrieval

Clinical records of all evaluated patients were reviewed to collect information concerning gender, gestational age (GA), postnatal age (PNA), body weight (BW), height, laboratory values, and medication.

Treatment with Sufentanil

Sufentanil (Sufentanil Torrex 5 µg/mL inj sol 5 × 2 mL) was adjusted in accordance with the summary of product characteristics. Initial bolus of 0.1–0.5 µg/kg i.v. was administered for 5–10 min, followed by a continuous infusion of 0.1–0.2 (0.5) µg/kg/h i.v. and titrated to appropriate level/effects. Other analgesedative drugs were administered based on international dosing recommendation protocols. Phenobarbital was administered as 15–20 mg/kg i.v. bolus over 5 min followed by 3–5 mg/kg/day dose split into 2 parts every 12 h. Midazolam was administered as 0.05–0.1 mg/kg i.v. bolus over 5 min followed by continuous infusion of 0.06–0.4 mg/kg/h to achieve desired effects in ventilated full-term neonates [14].

Analgesedation Efficacy and Safety

Drug dosing titration for pain management based on international recommendations and the protocolized analgesedation has

been introduced [15]. The analgesia/sedation was assessed every 3 h (or more often if needed) to individualize drug dosing. Pain and sedation assessments using a COMFORT-B score were done by trained nurses. Neonate with scores >22 or <11 was considered undersedated or oversedated, respectively [16–19].

PK Modelling

Sufentanil plasma concentrations (blood samples of 50–100 µL) were obtained as sparse sampling collections while time of samplings was precisely documented. Plasma concentrations of sufentanil were determined using a validated UPLC-MS/MS assay [20]. Individual sufentanil PK parameters – central compartment volume of distribution (V_{d_c}), total volume of distribution (Vd), CL, and distribution ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) – were calculated in a 2-compartmental PK model with first-order elimination kinetics based on individual demographic and clinical data and observed sufentanil plasma levels using MWPharm⁺⁺ software (MediWare, Prague, Czech Republic). The sufentanil PK data derived from Greeley et al. [4] (mean ± SD V_{d_c} , CL, $t_{1/2\alpha}$, and $t_{1/2\beta}$ of 4.15 ± 1.01 L/kg, 0.402 ± 0.366 L/h/kg, 0.39 ± 0.29 h, and 12.28 ± 5.77 h, respectively) were used for a priori simulation of the concentration-time profile in each patient. These simulated PK profile curves were a posteriori individualized to maximize fitting with observed concentration points. The fitting was performed using the Bayesian method. The goodness of fit was expressed using weighted sum of squares and root mean square values.

Data Analysis and Statistics

Optimal LD were calculated for each patient based on individual values of V_{d_c} using the following formula: LD (µg/kg) = Vd (L/kg) × C_{ss} (µg/L), where C_{ss} is 0.45 µg/L as a midpoint of the sufentanil target steady-state therapeutic range (0.3–0.6 µg/L). Optimal daily MD were calculated for each patient based on individual values of CL using the following formula: MD (µg/kg/h) = CL (L/kg/h) × C_{ss} (µg/L), where C_{ss} is 0.45 µg/L as a midpoint of the sufentanil target steady-state therapeutic range (0.3–0.6 µg/L) [21].

Descriptive parameters, median and interquartile range (IQR), were calculated using MS Excel 2010 (Microsoft Corporation, Redmond, WA, USA). The 95% confidence intervals (CI) for medians were calculated by the Bonett and Price [22] method. Linear regression models were used to evaluate the relationships of sufentanil PK parameters (V_{d_c} , $V_{d_{tot}}$, and CL) and patients' demographic characteristics (BW, GA, and PNA) using GraphPad Prism 8.2.1 software (GraphPad Inc., La Jolla, CA, USA). The same method was used to assess relationships between PK parameters or median levels of sufentanil and median COMFORT-B scores or proportions of COMFORT-B scores in the target range. *p* levels <0.05 were considered statistically significant.

Results

Study Population

Twelve (9 female and 3 male) neonates with median (IQR) BW of 3.18 (2.89–3.86) kg, GA of 39 (37–40) weeks, and PNA at the start of treatment of 9 (2–30) hours were included in the analysis. Demographic and clinical details

Table 1. Demographics and clinical characteristics of the population

Demography	
Age, h, at the start of treatment	9 (2–30)
GA, weeks	39 (37–40)
Birth BW, kg	3.17 (2.88–3.80)
Sex, female/male, <i>n</i> (%)	9/3 (75/25)
Survival, <i>n</i> (%)	10 (83)
Laboratory values at the start of treatment	
Creatinine, µmol/L	70.0 (66.0–77.0)
Urea, mmol/L	4.45 (3.05–5.9)
Total bilirubin, µmol/L	40.9 (32.9–73.6)
Direct bilirubin, µmol/L	6.75 (6.02–8.52)
Albumin, g/L	26.7 (25.9–28.8)
C-reactive protein, mg/L	1.0 (1.0–1.1)
Aspartate transaminase, IU/L	78.0 (12.9–110.4)
Alanine transaminase, IU/L	28.8 (14.4–44.1)
Concomitant treatments	
Ventilatory support, <i>n</i> (%)	12 (100)
Circulatory support, <i>n</i> (%)	11 (92)
Inotropics/vasopressors, <i>n</i> (%)	8 (67)
Midazolam, <i>n</i> (%)	10 (83)
Other analgesic/sedative drugs, <i>n</i> (%)	12 (100) [†]

Data are presented as median (IQR). GA, gestational age; BW, body weight. [†]From those, 12 neonates received phenobarbital, 2 phenytoin, and 1 clonidine and tramadol.

are presented in Table 1. Sufentanil dose ranged between 0.005 and 0.72 µg/kg/h. Duration of sufentanil treatment was 2–11 days.

Analgo-sedation Efficacy and Safety

In total, 509 COMFORT-B scores were obtained (16–57 per patient). There were 38.5% of COMFORT-B scores in the target range (11–22), while 61.3 and 0.2% were <11 and >22, respectively. No severe bradycardia and systemic hypotension were documented concerning the treatment with sufentanil.

Sufentanil Pharmacokinetics

In total, 232 sufentanil plasma levels were obtained with a median (range) number of samples of 19 (8–27) per patient. The distribution of sufentanil concentration points over the time is presented in Figure 1. PK analysis is summarized in Table 2. Median (IQR) weighted sum of squares and root mean square values were 12.61 (7.67–18.79) and 1.03 (1.01–1.07), respectively. We observed medium to high inter-individual variability of PK parameters normalized per kg of body weight demonstrated by a coefficient of variation of 25, 38, and 59% for Vd_c , Vd_{tot} , and CL, respectively.

Regression Models and Dosing Proposal

Linear regression models showed significant dependence of Vd_c (L) on GA ($r^2 = 0.3436$; $p = 0.0452$) and BW ($r^2 = 0.4019$; $p = 0.0268$). The other tested relationships were without statistical significance. Relationships between PK parameters and BW (for the purpose of dosing proposal) are demonstrated in Figure 2.

Median optimal sufentanil LD and MD calculated based on observed PK data were 2.13 (95% CI: 1.78–2.48) µg/kg and 0.29 (95% CI: 0.22–0.37) µg/kg/h, respectively. When we simulated administration of this LD on the model with each individual's PK data, 11 patients (92%) reached the target range for sufentanil concentrations (0.3–0.6 µg/L), while 1 patient (8%) was above the range. Simulation of the above-mentioned MD led to 6 patients (50%) in the target range, while 5 patients (42%) were above and 1 patient (8%) was under the range. There were no relationships between PK parameters or median levels of sufentanil and median COMFORT-B scores or proportions of COMFORT-B scores in the target range.

Discussion

Our work explored sufentanil disposition and dosage regimen for sufentanil in ventilated full-term neonates treated with sufentanil for prolonged analgesia. Overall, we have found PK parameters (Vd , CL, and $t_{1/2}$) similar to data published in neonates [4]. The highest inter-subject PK variability was shown for CL (59%) likely reflecting the ontogenetic maturation of elimination of sufentanil.

We reported similar PK parameters to data and trend published for paediatric population in intensive care units compared to normal children [3–5, 23]. Vd was reported large and CL decreased, and therefore $t_{1/2}$ prolonged, in neonates in comparison with young infants and older children [4, 7]. No data have been reported in preterm neonates except sufentanil dosage reduction in extremely low-birth-weight neonates after patent ductus arteriosus surgery [24]. For preterm neonates and neonates, low CL is expected as well as low protein binding (free fraction of sufentanil about 19.5%) and large variation in drug disposition compared to young infants and older children [4, 25].

Median optimal sufentanil LD and MD were calculated based on observed PK data. To calculate the optimal doses, we used the range of 0.3–0.6 µg/L as the PK target for efficacious and safe analgesia [21], while higher levels have been described for anaesthetic effects in the litera-

Fig. 1. Individual sufentanil concentration points over the time in 12 neonates.

Table 2. PK analysis of sufentanil in neonates

	Median	IQR	Range
Vd _c , L	15.5	13.2–17.9	6.3–25.4
Vd _c , L/kg	4.7	4.1–5.4	2.3–6.6
Vd _{tot} , L	39.5	24.4–49.7	17.4–71.0
Vd _{tot} , L/kg	11.8	7.7–15.4	6.3–18.2
CL, L/h	1.9	1.5–2.9	1.1–5.4
CL, L/h/kg	0.651	0.433–0.751	0.358–1.872
t _{1/2α} , h	0.0263	0.0260–0.0264	0.0230–0.0264
t _{1/2β} , h	13.3	9.4–16.7	5.18–21.3

PK, pharmacokinetic.

ture [26]. Currently, the usual induction and maintenance doses of sufentanil are 0.25–2.0 and 0.5–1.5 µg/kg/h, respectively [11, 27–29]. Our results indicate that the respective doses of 2.13 µg/kg and 0.29 µg/kg/h could be used. While the proposed LD is on the upper limit of the currently used dosing range, the MD is lower than

that currently considered, which corresponds to the relatively low CL of the drug in our study group, which was however similar to the previously published data. The doses are normalized to BW as a marker for maturation in this patient population [30, 31]. However, nonmaturational covariates inflammation and organ failure may also play important role in sufentanil drug disposition in neonates. Additionally, treatment modality (ECMO) superimposed on disease may lead to changes in sufentanil PK parameters [32]. Individual PK-based studies are generally conducted in order to describe PK parameters and determine the most prominent factors with highest potential to affect drug exposures. Although this individual approach leaves many possible sources of variability unexplored, the most important ones are generally better captured in limited sample size population provided that sufficient number of samples can be obtained. Our study population included frequent TDM data from 12 subjects. Due to the sample-rich database and relatively low span of the investigated covariates, we chose the individ-

Fig. 2. Relationship between sufentanil pharmacokinetic parameters (central volume of distribution (a), total volume of distribution (b), and clearance (c)) and body weight (for the purpose of dosing proposal).

ual-based approach. An advantage of our study is that it directly uses metrics and procedures that are a gold standard in routine clinical care and dose adjustments.

Limitation of this study is a small size of the investigated group since it deals with a very specific cohort. Our study has also not addressed PK/PD relationship. Although no relationship between sufentanil serum levels and COMFORT-B score has been noted, this is likely affected by comedication. No detailed PK/PD examinations have been conducted due to limited number of subjects. Furthermore, the proposal for LD and MD results from a PK analysis only and should thus be used for a prospective clinical trial to verify its efficacy and safety in routine clinical use.

In conclusion, BW and GA were found as covariates of sufentanil distribution. Sufentanil LD of 2.13 µg/kg and MD of 0.29 µg/kg/h should be verified in clinical trials for the use in ventilated full-term neonates treated for prolonged analgesia.

Statement of Ethics

The study was approved by the local ethics committee under the No. 2219/20 S-IV. At admission to the hospital, the patients' parents signed an approved general informed consent wherein

they state, inter alia, that anonymous data can be used for research. Exclusion criteria were refusal of general informed consent. Our study follows the principles of the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.P. and M.S. designed the study, P.P. gave the clinical support, B.K. performed laboratory diagnostics, P.P. and B.K. collected data, M.S. analysed data, P.P. and M.S. wrote the manuscript (original draft preparation), D.T. and O.S. wrote the manuscript (review and editing), and D.T. and O.S. gave conceptual advice. All coauthors have agreed to the submission of the final manuscript.

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