The Journal of Clinical Pharmacology
2016, 56(1) 109–115

DOI: 10.1002/jcph.577

Pharmacokinetics of Sufentanil During Long-Term Infusion in Critically Ill Pediatric Patients

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Abstract

The aim of this study was to develop a population pharmacokinetic model of sufentanil and to assess the influence of covariates in critically ill children admitted to a pediatric intensive care unit. After institutional approval, 41 children were enrolled in the study. Blood samples for pharmacokinetic (PK) assessment were collected from routinely placed arterial catheters during and after discontinuation of infusion. Population nonlinear mixed-effects modeling was performed using NONMEM. A 2-compartment model described sufentanil PK sufficiently. Typical values of the central and peripheral volume of distribution and the metabolic and intercompartmental clearance for a theoretical patient weighing 70 kg were $V_C = 7.90$ l, $V_T = 481$ L, $Cl = 45.3$ L/h, and $Q = 38.3$ L/h, respectively. High interindividual variability of all PK parameters was noted. Allometric/isometric principles to scale sufentanil PK revealed that to achieve the same steady-state sufentanil concentrations in plasma for pediatric patients of different body weights, the infusion rate should follow the formula (infusion rate for a 70-kg adult patient, μg/h) × (body weight/70 kg)$^{0.75}$. Severity of illness described by PRISM score, the monitored physiological and laboratory parameters, and coadministered drugs such as vasopressors were not found to be significant covariates.

Keywords

sufentanil, critical ill children, population PK, sedation

An opioid-benzodiazepine combination is one of the most commonly used analgosedation regimens in both adult and pediatric intensive care units (ICUs and PICUs).[1] Sufentanil is an opioid, often used in combination with midazolam, for prolonged sedation. It is highly selective for the μ-receptor and exhibits 5 to 15 times more potent action than fentanyl. Sufentanil is a short-acting highly lipophilic and highly protein bound (92.5%) agent. It is metabolized in the liver and to some extent in the small intestine, mainly by the CYP3A4 enzyme.[2] Following intravenous administration, sufentanil disappears from the body in a triexponential fashion with a terminal half-life of about 2.5 hours.[1] Ethuin et al showed, that both the terminal half-life and the volume of distribution may be increased after prolonged infusion, at least in adult ICU patients.[3] Literature data concerning the pharmacokinetics of sufentanil in children are limited, as most experience with sufentanil comes from pediatric anesthesia practice, whereas limited data concerning sufentanil pharmacokinetics in PICU population are available. Guay et al[4] performed a study in ASA I and II status patients between 2 and 8 years old scheduled for elective anesthesia and surgery. The pharmacokinetics of sufentanil after a single bolus administration showed that both the distribution and the elimination half-life were shorter when compared with adult patients.[3] Other studies described[5–8] patients undergoing cardiovascular surgery and patients with chronic renal insufficiency undergoing noncardiac surgery. They were reviewed by Lundeberg et al[1] (Supplemental Table 1S). In all these 3 studies, clearance (per kilogram of body mass) was 2- to 3-fold lower than in healthy children. To our knowledge, no studies concerning the pharmacokinetics (PK) of long-term infusion of sufentanil in critically ill children staying in the ICU have been published.

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Submitted for publication 25 March 2015; accepted 17 June 2015.

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The PK of sufentanil in PICU patients may be influenced by maturation, body weight, duration of infusion, and patients' clinical conditions, such as severity of illness (PRISM), the presence/absence of sepsis, heart failure, renal or liver failure, and coadministered drugs. Therefore, the aim of this study was to develop a population pharmacokinetic model of sufentanil for pediatric patients.

Materials and Methods

Patients

After obtaining institutional Bioethics Committee approval (No. 329/11), this open-label prospective study was started. Written informed consent was obtained from parents or legal representatives. Forty-one patients between 0 and 18 years of age were enrolled in the study. For every patient, the study started during the first 24 hours of the stay in the PICU. All patients required mechanical ventilation for at least 24 hours. Indications for analgesia and sedation were mainly the use of mechanical ventilation due to respiratory failure after operation (n = 15), severe respiratory insufficiency during the course of severe sepsis or septic shock (n = 17), multiple trauma or traumatic brain injury (n = 7), or cardiac arrest (n = 2). Exclusion criteria included the following factors: age >18 years, known allergy to sufentanil, usage of neuromuscular blocking agents, and severe renal and/or hepatic insufficiency with serum bilirubin and creatinine levels 2-fold higher than upper limits of normal reference values.

During the enrollment, every patient was evaluated according to the Pediatric Risk of Mortality Score (PRISM). Sedation monitoring was carried out according to Cook Scale, which is routinely used in our department, and the PICU team has been trained in the use of this score (Supplemental Figure 1S).[11–13] The first assessment was done just after the beginning of the infusion of sufentanil, then at every moment of blood sample collection for clinical reasons, and subsequently routinely every 6 hours daily. Among the children with postoperative respiratory insufficiency and severe respiratory failure during the course of sepsis or septic shock, 19 of 32 patients (59.4%) needed norepinephrine support in dosages from 0.01 to 0.1 μg/kg per minute. After cardiac arrest, 2 patients were treated with norepinephrine at an average dose of 0.08 μg/kg per minute. In turn, 5 children after the trauma (71.4%), needed norepinephrine support at the same rate as the first 2 groups. The exact protocol is provided in the Supplemental Materials.

Patient-Related and Analytical Procedures

Blood samples for PK assessment (2 mL) were collected from the arterial catheter. The first blood sample was taken just before the start of sufentanil infusion, the second after 3 hours of infusion and then every 24 hours. When the sufentanil infusion was stopped, blood samples were taken in 0 (eg, just before the stop), 3, 5, 20, 40, 60, and 120 minutes and then at 6, 12, and 36 hours. The blood samples were centrifuged immediately after collection, and the plasma was stored at −70 °C until assay. The details about the drug assay method are given in the Supplemental Materials.

PK Model

Population nonlinear mixed-effects modeling was performed using NONMEM software (version 7.2.0; ICON Development Solutions, Ellicott City, Maryland), and the gfortran compiler 9.0. NONMEM runs were executed using Wings for NONMEM (WFN720; http://wfn.sourceforge.net). The first-order conditional estimation with interaction method was used. The NONMEM data processing and plots were done in Matlab Software (version 7.13; MathWorks, Natick, Massachusetts).

Plasma sufentanil concentrations were described by means of a 2-compartment model using ADVAN6 subroutine with C_P, C_T denoting concentrations of sufentanil in the central and peripheral compartments. The model was parameterized with volume and clearance terms. V_C and V_T denote volumes of distribution of the respective compartments. CL and Q denote the metabolic and the intercompartmental clearance of sufentanil. The proportional residual random error was used. Interindividual variability (IIV) for all PK parameters was modeled assuming a log-normal distribution.

Covariates Search and Allometric/Isometric Scaling

The main aim of this study was to examine the potential effect of various covariates (listed in Table 1) on sufentanil PK. Specifically, the effect of body size on all the volume (V_C, V_T) and clearance (CL, Q) parameters was included based on allometric/isometric scaling as follows:

$$P_i = P_{pop}\left(\frac{BW_i}{70}\right)^K \exp(\eta_{P,i})$$

where P_i denotes the individual value of volume and clearance term, P_{pop} is the population estimates of volume and clearance terms, BW_i is the individual body weight, 70 is the typical body weight of adult patients in kilograms, and K is the exponent equal to 0.75 for clearance and 1 for distribution volumes.[14] Further details about covariate analysis is provided in the Supplemental Materials.

Model Evaluation

The minimum value of the NONMEM objective function, typical goodness-of-fit diagnostic plots, evaluation of the

Table 1. Demographic Characterization of Patients (Results Expressed as Median and Range)

Parameter (Unit)	Median (Range or Number) (n = 41)
Age (years)	4.05 (0.18–17.4)
Weight (kg)	14 (3.2–80)
Height (cm)	96.5 (52–185)
Male/female	23/19
Pediatric Risk of Mortality Score (PRISM)	11 (5–39)
Stay in PICU (days)	18 (3–68)
Indication to PICU (%)	
Severe sepsis or septic shock	17 (41.5%)
Major noncardiac surgery	15 (36.6%)
Multiple trauma or traumatic brain injury	7 (17.1%)
Cardiac arrest	2 (4.8%)
Use of norepinephrine (yes/no)	25/16
Severe sepsis or septic shock	9/7
Major surgery	9/7
Multiple trauma or traumatic brain injury	5/2
Cardiac arrest	2/0
Sufentanil total dose (μg)	2197 (621–47 221)
Sufentanil infusion rate (μg/kg per hour)	1.42 (0.47–4.39)
Sufentanil infusion duration (hours)	99 (25–600)
Successful extubation/reversed to tracheostomy	36/5
Death rate (%)	4 (9.8%)

precision of PK parameter, variability via bootstrap technique,[15] and assessment of shrinkage[16] were used to discriminate between various models during the model-building process. The model performance was assessed by means of visual predictive check and normalized prediction distribution errors.[17] Further details about each method are provided in the Supplemental Materials.

Context-Sensitive Half-Time

The context-sensitive half-time and context-sensitive 75% decrement time were obtained based on the typical parameter estimates of our final PK model. They were calculated using computer simulation as the time needed for a 50% and 75% decrease in anesthetic concentration after an infusion regimen designed to produce a constant level of sufentanil concentrations, as described in the original references.[9,18]

Results

This analysis was based on the concentration–time profiles of sufentanil collected from 41 PICU children. Table 1 lists the patients' demographic, clinical laboratory, and vital sign characteristics. Figure 1 shows the available sample data, consisting of 363 sufentanil concentration measurements collected during the median (range) duration of infusion of 99 hours (25–600 hours).

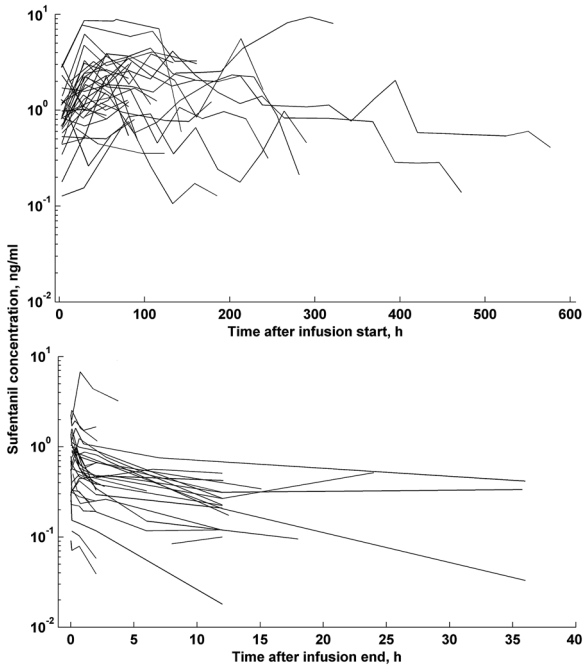

Figure 1. Individual sufentanil concentration–time profiles.

The median (range) plasma concentration of sufentanil 3 hours after infusion start was 0.826 ng/mL (0.127–3.03 ng/mL). It increased to a median (range) of 1.438 ng/mL (0.361–6.93 ng/mL) observed throughout the infusion. After infusion cessation, the sufentanil concentrations declined, although in about half the patients an increase in plasma concentration was observed, suggesting the presence of a second peak. A median (range) 19.0% (1.29%–240%) elevation of plasma sufentanil concentration above its previous value was noted in this study. It occurred fairly early, at a median time of 0.083 hours (0.006–8 hours) after the infusion was stopped.

One-, 2-, and 3-compartment models with and without maturation functions were screened during the model-building process. A 2-compartment model, developed after implementation of allometric scaling to all clearance and isometric scaling to all volume of distribution parameters turned out to be sufficient to describe our data. We failed to propose the model for secondary peaks, very likely because those peaks are small and occur at different times after infusion cessation.

Table 2 provides the final parameter estimates along with bootstrap results. All parameters and intersubject and residual error variances were estimated with low (lower than 50%) coefficients of variation (CVs). The shrinkage was low (5%) for clearance, moderate for volume of distribution (19%), and high for distribution clearance and volume of central compartment (38% and 100%, respectvively). For the last 2 parameters, the data were not informative with regard to interpatient variability.

Table 2. Parameter Estimates of the Final PK Model of Sufentanil (Bootstrap Estimates Given for Comparison)

Parameter (Unit)	Estimate (%CV) [Shrinkage]	Estimate, Bootstrap Median [5th-95th CI]
θ_{VC} (L)	7.90 (38.1) · (BW/70)	7.77 [1.6–68.4] · (BW/70)
θ_{CL} (L/h)	45.3 (7.9) · (BW/70)$^{0.75}$	45.1 [39.5–52] · (BW/70)$^{0.75}$
θ_{VT} (L)	481 (18.7) · (BW/70)	464 [334–724] · (BW/70)
θ_{Q} (L/h)	38.3 (14.6) · (BW/70)$^{0.75}$	37.1 [24.8–51.5] · (BW/70)$^{0.75}$
Between-subject variability		
ω^2_{VC} (%CV)	0 FIX [100]	0 FIX
ω^2_{CL} (%CV)	48.9 (31.7) [4.9]	47.8 [34.2–59.3]
ω^2_{VT} (%CV)	120 (33.3) [18.9]	117 [82.3–160]
ω^2_{Q} (%CV)	61.0 (41.1) [37.6]	58.1 [18.2–81.2]
Residual error model		
$\sigma^2_{prop,\ Cp}$ (%CV)	36.9 (5.1) [8.9]	36.5 [32.8–39.8]

The typical value of the volume of the central compartment (V_C) scaled to 70 kg was close to a plasma volume of 7.90 L, whereas the volume of the peripheral compartment was very high ($V_T = 481$ L). The typical systemic clearance (CL) of sufentanil and the distribution clearances were 45.3 L/h (10.8 mL/kg per minute) and 38.3 L/h for a patient with a weight of 70 kg. The IIV was estimated for the CL, V_T, and Q, for which was 49%, 120%, and 61%, respectively. For the V_C it tended toward zero during the model-building process.

The median (range) half-life corresponding to alpha phase was 2.60 minutes (1.24–5.80 minutes), and the median (range) beta-phase half-life was much longer and highly variable — 8.40 hours (1.7–205 hours).

The children enrolled in this study had great differences in body weight, ranging from 3.2 to 80 kg. In this study the allometric/isometric scaling with theory-based exponents for all clearance and volume terms was used. The inclusion of allometric/isometric scaling and correlation between parameters led to a substantial drop in the NONMEM objective function of 71.6. Body weight explained about 36% of variability for CL, Q, and VT. Possible relationships between other patient-specific covariates (age, sex, PRISM, total dose, infusion duration, systolic blood pressure, diastolic blood pressure, heart rate, temperature, total protein, cholesterol, triglyceride, hematocrit, pH, pCO_2, pO_2, alanine aminotransferase, aspartate aminotransferase) and the individual PK parameter estimates were explored by graphical analysis. None of the covariates were found to be statistically significant in this study, as there was no clear relationship between them and individual PK parameter estimates. The relationship between body weight–normalized clearance and age is shown in Figure 2. There was a tendency for CL/BW to decrease with age. This was well accounted for by the allometric scaling, as no trend was visible for CL/(BW**0.75).

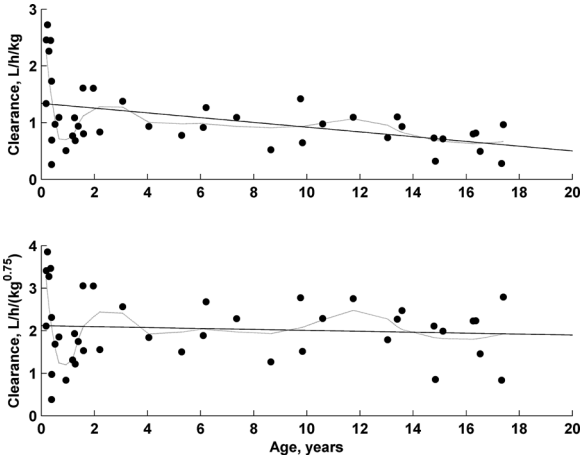

Figure 2. Relationship of body weight–normalized clearances (CL/F/BW and CL/F/[BW**0.75]) versus age for all patients in the study. The loess smooth (dotted) and regression (solid) lines were added to indicate the trend in the data.

Figure 3 presents context-sensitive half-time (CSHT) and context-sensitive 75% decrement time (CSDT) for 3 typical children weighing 10, 30, and 70 kg in relation to the duration of infusion. CSHT for sufentanil increased, reaching a plateau for infusion durations longer than 40–50 hours. For long infusions the maximal CSHT was 9, 11, and 14 minutes for children weighing 10, 30, and 70 kg, respectively. For shorter infusions, it was low and ranged from 2.5 to 4 minutes. On the other hand, CSDT was much larger. For short infusions, CSDT ranged from

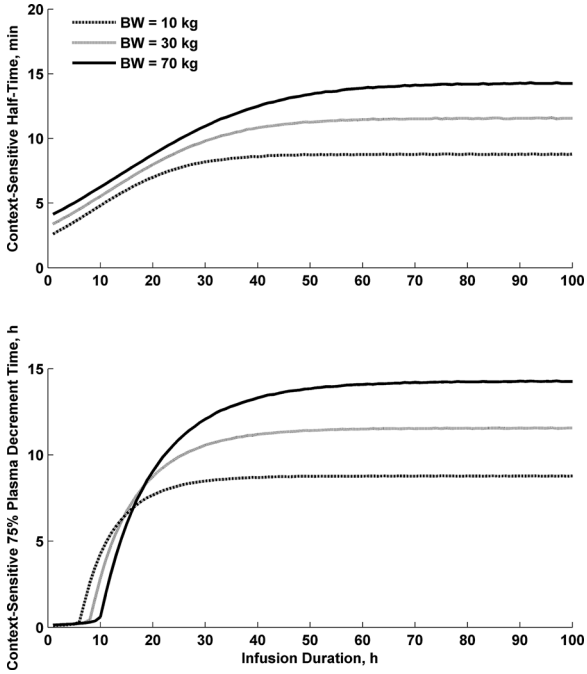

Figure 3. Context-sensitive half-time and context sensitive 75% decrement time in relation to the infusion duration for 3 typical children of 10, 30, and 70 kg body weight.

5 to 10 minutes. For infusion longer than 6 hours, it steeply increased, reaching a plateau at 40–50 hours of 8.7, 11.5, and 14 hours for children weighing 10, 30, and 70 kg, respectively.

The median (range) postinfusion time of extubation for our patients was 11 hours (1–74 hours). The median (range) plasma sufentanil concentrations were obtained from the individual prediction of the final model and was 0.25 ng/mL (0.00006–2.81 ng/mL).

Discussion

To our knowledge, the current study is the first assessing the pharmacokinetics of long-term infusion of sufentanil in children admitted to a PICU. The median (range) infusion rate required in our patients was 1.42 μg/kg per hour (0.475–4.39 μg/kg per hour) for the median (range) duration of 99 hours (25–600 hours). There were no statistically significant ($P < .05$) differences in average infusion rates between the 4 groups (respiratory failure, severe sepsis or septic shock, multiple trauma or traumatic brain injury, and cardiac arrest). The infusion rate of this study was slightly higher than the mean infusion rates of sufentanil used by Wappler et al (1.2 [0.09–2.7] μg/kg per hour)[19] during sufentanil/midazolam analgosedation. Other investigators[20,21] reported lower doses of 0.5 μg/kg per hour during mechanical ventilation for more than 96 hours, achieving satisfactory levels of hypnotic and analgesic potency. The dosing regimen applied in this study was also higher than that used by Ethuin et al,[3] who studied the pharmacokinetics of sufentanil in adult ICU patients (0.8 μg/kg per hour). Nevertheless, the higher infusion rate for children can be expected by children (especially infants) having a higher clearance when expressed per kilogram of body weight.

Patient size (as reflected by body weight), patient maturation (as reflected by age), and infusion parameters are often considered important factors influencing drug pharmacokinetics. Our study suggests that the age dependence of sufentanil PK parameters is very well accounted for by consideration of body weight only for age ranging from 1 to 18 years. Thus, body weight dosing based on allometric principles should be preferred to get the same drug concentration in plasma across different age groups. In other words, to achieve the same steady-state sufentanil concentrations in plasma for patients of different body weights, the infusion rate should follow the formula (infusion rate for a 70-kg patient, μg /h) × (body weight/70 kg)$^{0.75}$. In our study no newborns were included, as the youngest patient was 2 months old. Nevertheless, for very young children (neonates and infants), the pharmacokinetics of sufentanil can be expected to vary with age, as demonstrated for other drugs such as midazolam.[22] It is a consequence of the maturation of the hepatic microsomal oxidizing system that leads to considerable changes in drugs metabolic clearance in the first 2 years of life.[23,24] Our data did not show any age-related changes because of the small number of very young children (9 of them were younger than 1 year). Interestingly, sex, infusion duration, severity of illness status as described by PRISM scale, type of disease, but also monitored physiological (heart rate, blood pressure) and laboratory parameters and comedication such as vasopressors, were not found to significantly influence sufentanil PK.

The comparison of literature clearances for children and adults was done using allometric scaling to a common standard (like 70 kg) as proposed earlier by Holford et al[15,25] and is presented in Supplemental Table 1S. In our study a value of systemic clearance scaled to 70 kg (10.8 mL/kg per minute) was about 2 times lower than that presented in the study performed on healthy children (ASA I–II) treated with a single bolus of sufentanil (0.9 to 3.0 μg/kg), in whom a value of 22.6 mL/kg per minute was found.[4] Interestingly, all other studies noted the comparable clearances: in surgical patients receiving a sufentanil bolus at a dose of 5 μg/kg per hour intravenously (12.7 ± 0.8 mL/kg per minute),[26] children with cardiovascular surgery,[5–8] and adult patients (7.4 and 15.0 mL/kg per minute).[27,28] Also Ethuin et al,[3] who studied the pharmacokinetics of sufentanil in adult ICU patients under a similar experimental design, obtained a comparable clearance value of 13.4 ± 7.0 mL/kg per minute.

The volume of distribution at steady state (6.98 L/kg) fell within the range of values observed in children and adults (1.3–22.6 L/kg) reported in the literature (Table 1S).[3–6,8,26–28]

The concentration of an opioid drug is an important factor in determining the risk of respiratory depression, which has not been well established, but it is considered for concentrations of sufentanil exceeding 0.25 ng/mL.[10] In this study the opioid concentrations during the infusion were about 6-fold higher than this value. On the cessation of infusion, the sufentanil concentration in the plasma declines, leading to the question of when the drug reaches the concentration, which ensures safe extubation of the patient. For our patients, the median extubation time occurred at 11 hours and at a sufentanil plasma concentration of 0.25 ng/mL. Surprisingly, the extubation occurred at sufentanil concentrations ensuring proper respiratory function, as has already been postulated in the literature.[10]

The CSHT and CSDT were obtained to illustrate the weight dependence of the sufentanil decline after stopping the infusion (Figure 3). Both the CSHT and CSDT are higher for heavier patients. This trend is also well explained by allometry, as the half-life, the major determinant of half-time, scales with body weight

according to $(BW/70)^{0.25}$. So, a moderate increase along with body weight is expected. The CSHT shows that the decrease in sufentanil concentrations by half lasts less than 15 minutes after a dosing regimen, ensuring a constant concentration. It is a slightly lower value than that presented in the literature for adults, in which it is about 50 minutes for a duration of infusion comparable to that used in this study.[9,29] On the other hand, a decrease in the final concentration by 75% requires a much longer time (about half a day), as illustrated by the CSDT. Thus, the CSDT should be taken into consideration as an important determinant of the patient's extubation time. It also underlines the importance of terminal half-life in the reversibility of sufentanil infusion, as Ethuin et al[3] suggested for adults.

The presence of secondary peaks has been reported for sufentanil, fentanyl, and propofol between the first and second hour after the end of infusion.[27,30,31] It was also observed among the patients undergoing anesthesia with propofol, where Knibbe et al described the presence of secondary peaks at the moment of or directly after extubation in 67% of patients.[32] It is mostly anticipated that this phenomenon occurs with alterations in blood flow during the patient's awakening, following redistribution of the drug from fat tissue.[33] The appearance of the postinfusion peak in children poses a question about the patient's safety during long-term opioid management, especially in the youngest age group. This is also consistent with the findings by Geller et al, who observed severe respiratory depression in adult patients after major abdominal surgery more frequently after intravenous than after epidural administration, although equipotent analgesic doses of sufentanil were used.[20] Moderate to deep sedation and respiratory depression occurred soon after the start of intravenous infusion of sufentanil, but not after the epidural infusion, reaching plasma concentrations of more than 300 pg/mL. The issue of the use of long-term infusion of sufentanil in children treated in a PICU is even more important in view of the increased risks of side effects, especially respiratory depression. Nevertheless, our data show that the second peaks are low, and they occur early after the end of infusion, when patients are still in the ICU settings. Thus, they can be considered clinically insignificant.

Conclusions

A population PK model was successfully developed to describe the time course and variability of sufentanil in PICU patients using allometric principles. The disease status described by PRISM score, the monitored physiological and laboratory parameters, and other coadministered drugs such as norepinephrine were not found to be independently significant covariates in this study.

Acknowledgments

The authors thank Professor Catherijne Knibbe of the Faculty of Science, Leiden Academic Centre for Drug Research, Pharmacology, The Netherlands, for her invaluable advice. This project was partially supported by grant 2014/15/N/NZ7/03028 funded by Polish National Science Centre.

Declaration of Conflicting Interests

None to declare.

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