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ORIGINAL

Pharmacokinetics of long-term sufentanil infusion for sedation in ICU patients

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Abstract *Objective:* To determine the pharmacokinetics of long-term infusion of sufentanil in ICU patients. *Design and setting:* Open-label study in a surgical intensive care unit. *Patients:* Ten consecutive patients without renal or hepatic failure requiring mechanical ventilation for at least 6 days. *Interventions:* Patients received sufentanil (initial bolus 0.5 μg/kg and continuous infusion rate of 0.5 μg/kg per hour) and midazolam (initial bolus 0.08 mg/kg and continuous infusion 0.05 mg/kg per hour). Sedation was adjusted according to the Ramsay scale (score >3). Blood samples were taken during and up to 72 h after the infusion, and plasma concentrations were measured using a sensitive radioimmunoassay method. *Measurements and results:* Plasma concentration-time profiles of sufentanil and pharmacokinetic parameters such as initial postinfusion half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$), total clearance (Cl), volume of distribution (Vdβ), and time required to obtain a 50% decrease in plasma concentration ($tcp_{0/2}$). The mean duration of sedation was 12±7 days. The initial half-life $t_{1/2\alpha}$ was 1.33±1.15 h. The observed prolonged elimination half-life ($t_{1/2\beta}$=25.5±9.4 h) was related to the large volume of distribution (Vdβ=22.6±9.4 l/kg). The mean total clearance was 13.4±7.0 ml/kg per minute. The mean time required to obtain a 50% decrease in plasma concentration was short ($tcp_{0/2}$=4.7±3.7 h). *Conclusions:* The pharmacokinetic analysis of sufentanil for ICU sedation revealed increased volume of distribution and elimination half-life. Nevertheless the rapid distribution and elimination processes suggest that the rapid reversibility of sedation with sufentanil is maintained after long duration of infusion. Further studies should be carried out to evaluate the clinical relevance of these results.

Keywords Sufentanil · Pharmacokinetics · Intensive care · Sedation

Introduction

Critically ill patients often require sedation to treat anxiety or agitation and to control noxious stimuli. A short-acting benzodiazepine such as midazolam is commonly used in the ICU, but this does not provide analgesia, and continuous infusion of midazolam may lead to accumulation and delayed recovery [1]. An opiate-benzodiazepine combination is therefore the most frequently sedation regimen used in Western European ICUs [2]. Morphine and fentanyl have unfavorable pharmacokinetics when given by prolonged continuous infusion [3]. However, computer simulations suggest clinical advantages of sufentanil infusions [4]. The pharmacokinetic profile of sufentanil has been determined during general anesthesia [5, 6, 7], and sufentanil has been used for short-term sedation [8, 9]. Its rapid distribution and high clearance could prevent accumulation when given for a long

Table 1 Characteristics of study patients (*SAPS II* Simplified Acute Physiology Score II, *ARDS* acute respiratory distress syndrome)

Patient no.	Diagnosis	Age (years)	Weight (kg)	SAPS II	Sufentanil (μg kg^{-1} h^{-1})	Midazolam (mg kg^{-1} h^{-1})	Sedation time (days)
1	Mediastinitis	50	76	40	0.74	0.05	8
2	ARDS	60	82	34	1.90	0.08	9
3	ARDS	67	77	33	0.52	0.06	18
4	Gastric inhalation	43	77	30	2.09	0.15	23
5	Trauma	69	86	30	0.34	0.07	21
6	Peritonitis	61	74	37	0.33	0.05	6
7	Pneumonia	33	70	13	0.42	0.05	6
8	Peritonitis	60	81	52	0.85	0.07	6
9	Acute pancreatitis	60	77	33	0.72	0.13	9
10	ARDS	60	62	49	0.46	0.07	12
Range	–	33–69	62–86	13–52	0.33–2.09	0.05–0.15	6–23
Mean±SD	–	56±11	76±7	35±12	0.80±0.60	0.08±0.04	12±7

time, but only limited pharmacokinetic data are available during long-term sedation of ICU patients. The goal of this study was to determine the pharmacokinetic profile of sufentanil in ten patients requiring ventilation and sedation for several days in the ICU.

Patients and methods

Patients

After obtaining institutional ethics review board approval and informed consent from family members this open study enrolled ten consecutive patients admitted to the ICU who required prolonged controlled mechanical ventilation after surgery. The procedures were conducted in accordance with the Declaration of Helsinki principles. Exclusion criteria were a history of alcohol or drug abuse, impaired renal or hepatic function, pregnancy and age under 18 years. Fourteen patients were originally included in this open trial; four of these were subsequently withdrawn (one died, one required hemodialysis, and two required less than 3 days of mechanical ventilation). The final study group thus consisted of ten men aged 33–69 years (mean 56±11) and weighting 70–86 kg (mean 76±7). Table 1 summarizes the patients' demographic and clinical characteristics. No agents known to alter sufentanil metabolism by cytochrome P450 (cimetidine, omeprazole, macrolides, and azole antifungal drugs) were given to the patients. Clinical status was assessed by the Simplified Acute Physiology Score II on the day of ICU admission [10].

Protocol

The sedative protocol was as follows: sufentanil was given as a single intravenously bolus of 0.5 μg/kg over 3 min. The drug was then administered by continuous infusion at a constant rate of 0.5 μg/kg per hour. Infusion rate adjustments were made by increments of 0.2 μg/kg per hour to achieve no pain (by communicating with the patient whenever it was possible or by combination of clinic criteria indicating inadequate analgesic therapy). Concomitantly patients received a continuous infusion of 0.05 mg/kg midazolam per hour, preceded by a loading dose of 0.08 mg/kg over 15 min. The infusion rate was adjusted to keep the patient comfortable and somnolent but arousable and a Ramsay score of at least 3 ("responds to commands only") [11]. Sufentanil infusion was withdrawn if the patient's clinical status was judged compatible with ventilation weaning.

Plasma sampling

To follow sufentanil concentrations in plasma during long-term infusion the arterial blood samples (7 ml each) were withdrawn at 8 a.m. and 6 p.m. every day throughout sufentanil administration and 10, 20, 40 min and 1, 2, 6, 12, 36, 48, 60, 72 h after the end of the infusion. Blood was collected in heparinized tubes and then centrifuged for 10 min at 2,500 rpm. Plasma was separated and stored at −20°C until assay. Sufentanil concentrations were determined in duplicate by the Janssen Research Foundation (Val de Reuil, France), by means of radioimmunoassay [12] with a detection limit of 0.05 ng/ml plasma after selective solvent extraction (*n*-heptane/isoamyl alcohol, 98.5/1.5 v/v). Interassay precision and accuracy were 11.4% and 99.9%, respectively, based on quality-control samples at three concentrations (0.05, 0.2, and 1 ng), and 5.2±1.9% and 100.5±2%, respectively, based on calibration curves for a concentration range of 0.05±0.4 ng/ml.

Pharmacokinetic analysis

Plasma sufentanil concentrations during the continuous infusion and the postinfusion period were used to calculate the area under the concentration-time curves (AUCt) using the trapezoidal rule, with extrapolation to infinity ($AUC\infty = AUCt + Ct/\beta$, where Ct is the last measured concentration and β the exponent of the last exponential term). The average plasma concentration (Cav) was determined from the plasma concentrations measured on the apparent plateau during the infusion. Cav_{ad} is the average concentration adjusted to the initial infusion rate of 0.5 μg/kg per hour. Plasma concentration-time curves after the end of the infusion were fitted using a weighted least squares algorithm, with the weighting factor 1/y calculated^2 (SIPHAR software, Simed, Paris, France) to obtain initial ($t_{1/2\alpha}$) and terminal ($t_{1/2\beta}$) half-lives. Estimated times required to obtain a 50% decrease in plasma concentrations ($tcp_{0/2}$) were calculated from the exponential equation of the fitted plasma decay curves. Total clearance (Cl) and the total volume of distribution (Vdβ) were calculated by using standard methods, from the formulas $Cl = Dose/AUC\infty$, and $Vd\beta = Cl/\beta$ [13]. Results and pharmacokinetic parameters are expressed as means ±standard deviation or ranges.

Results

Table 1 presents the individual duration of sedation and infusion rates of sufentanil and midazolam. To achieve adequate analgesia and sedation patients required mean

Table 2 Pharmacokinetic parameters for sufentanil [*Cav* average plasma concentration during the infusion, Cav_{ad} Cav adjusted to the infusion rate (0.50 μg kg^{-1} h^{-1}), *Cl* total clearance, *Vdβ* total volume of distribution in the β phase, $t_{1/2\alpha}$ initial postinfusion half-life, $t_{1/2\beta}$ terminal half-life, $tcp_{0/2}$ estimated times required for a 50% decrease in plasma concentrations, *na* not available (plasma level below the quantification limit)]

Patient no.	Cav (ng/ml)	Cav_{ad} (ng/ml)	Cl (ml min^{-1} kg^{-1})	VDβ (l/kg)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$tcp_{0/2}$ (h)
1	0.73	1.08±0.15	11.0	25.6	4.23	26.9	6.4
2	0.33	1.25±0.33	24.3	33.7	0.75	16.1	1.8
3	1.00	1.04±0.17	7.6	26.3	2.02	40.1	12.0
4	0.58	2.43±0.64	15.4	17.6	0.55	13.2	1.6
5	2.29	1.56±0.51	6.8	22.9	1.50	38.8	4.6
6	0.58	0.38±0.16	11.9	32.6	0.33	31.6	8.5
7	1.45	1.22±0.68	6.3	11.8	0.57	21.6	1.3
8	0.56	0.95±0.25	16.1	32.9	0.67	23.5	1.4
9	0.79	1.14±0.16	9.0	16.3	1.16	21.0	4.9
10	0.3	0.28±0.14	25.9	na[1]	1.58	na	na
Mean ±SD	0.86±0.60	1.13±0.6	13.4±7.0	22.6±9.4	1.33±1.15	25.5±9.4	4.7±3.7

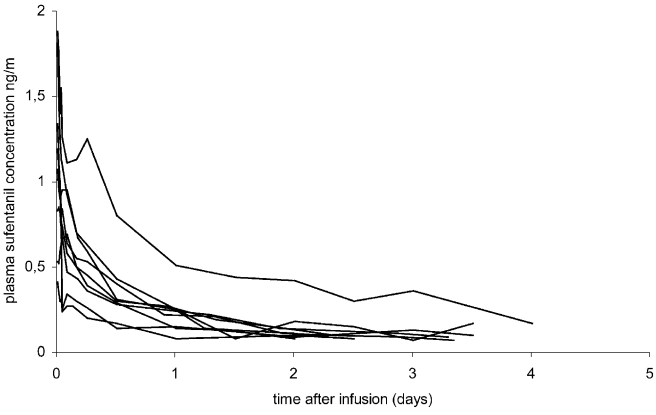

Fig. 1 Individual sufentanil plasma concentration decay curves after stopping continuous infusion

hourly doses of sufentanil at 0.8 μg/kg and midazolam at 0.08 mg/kg. In five patients the sufentanil infusion rate remained the same or was lower than the initial rate. The other five patients received boluses before infusion rate increments. Only one or two supplementary boluses were required to achieve a new adequate level of sedation, and infusion rates then remained stable until sufentanil discontinuation. After the end of the infusion the plasma sufentanil concentration-time curves were best described by a two-compartment model, with a initial distribution phase $t_{1/2\alpha}$ of 1.33±1.15 h and a terminal elimination phase $t_{1/2\beta}$ of 25.5±9.4 h. Our analysis yielded a total volume of distribution of 22.6 l/kg, a total clearance of 13.4 ml/kg per minute and an estimated time required to obtain a 50% decrease in plasma concentrations $tcp_{0/2}$ of 4.7±3.7 h (Table 2). The individual plasma concentration-time curves after discontinuation of the infusion are illustrated in Fig. 1. Except for one patient at day one after stopping infusion no secondary peaks were observed during the sufentanil elimination phase.

Discussion

The goal of this study was to establish the pharmacokinetic profile of sufentanil administered by continuous prolonged infusion to ICU patients requiring sedation for mechanical ventilation. By chance, only male patients were included, but it has not been reported in the literature that gender can affect the pharmacokinetics of sufentanil. The mean dose required by the patients in our study (0.8 μg/kg per hour) was in accordance with data published by other authors. Hofbauer et al. [8] used 0.75–1.0 μg/kg per hour sufentanil with midazolam in patients requiring mechanical ventilation for more than 96 h. Wappler et al. [9] used 0.4–1.5 μg/kg per hour sufentanil in combination with midazolam for sedation of ICU patients. Compared to short-course administration, the main findings are that the terminal half-life ($t_{1/2\beta}$) was found prolonged and the apparent volume of distribution in the β phase (VDβ) increased. Nevertheless the total clearance was similar to that reported in anesthetic practice [5, 6, 7]. More importantly, the sufentanil plasma concentration fell rapidly, starting immediately after the end of the infusion, regardless of the duration of administration, accounting for a short initial phase $t_{1/2\alpha}$. In the postinfusion period the time required for a 50% reduction in the plasma concentration measured at the end of the infusion was 4.7±3.7 h.

During the infusion period the average plasma level (Cav_{ad}) was 1.13±0.6 ng/ml, with wide interindividual variability (range 0.28–2.43). However, plasma sufentanil concentrations in each patient appeared to plateau when optimal sedation was obtained. As the sufentanil infusion rate was adjusted individually to keep the patient comfortable, the average real steady-state concentration (Css) was not calculated.

We observed a longer elimination half-life and a larger volume of distribution than with a single sufentanil bolus in the surgical setting. Lehman et al. [7] studied

the pharmacokinetics of sufentanil in 56 patients after a 2 μg/kg bolus in combination with droperidol or volatile anesthetics and reported an elimination half-life ($t_{1/2\beta}$) of 3.0±1.0 h and a volume of distribution of 3.4±1.9 l/kg. Chauvin et al. [14] reported a $t_{1/2\beta}$ of 3.5±0.9 h and a Vdss of 3.3±0.7 l/kg after a 3 μg/kg bolus. Finally, Bovill et al. [5] reported a $t_{1/2\beta}$ of 2.7±0.4 h and a Vdss of 1.7±0.2 l/kg after a bolus of 5 μg/kg. These differences in sufentanil pharmacokinetics in our study could be attributed in part to changes in protein binding, tissue distribution, and/or hepatic clearance as shown in ICU patients. Nevertheless, as pointed out by Gepts et al. [4], these studies involved relatively short sampling periods (no longer than 10 h), and sufentanil pharmacokinetics differ strictly in relation with different sampling periods. These authors studied 23 surgical patients who received sufentanil as a short infusion (10–20 min). Mean terminal half-lives ranged from 3.4 to 16.6 h and Vdss values from 2.7 to 5.2 l/kg after sufentanil doses of 250–1500 μg. More recently Brusset et al. [15] used the same type of pharmacokinetic analysis and reported a long terminal half-life (21±12 h) and a large Vdss (8.7±3.9 l/kg). These authors sampled blood for about 30 h after a 15 μg/kg bolus. These results suggest that sufentanil levels must be measured for at least 24 h to obtain an accurate terminal half-life and total volume of distribution. We obtained a longer terminal half-life ($t_{1/2\beta}$=26 h) than Gepts et al. [4] and Brusset et al. [15] (16 and 21 h, respectively) probably because of our larger volume of distribution (Vdβ=23 vs. 15 l/kg calculated from the data of Gepts et al. and Brusset et al). Few authors have investigated the pharmacokinetics of sufentanil in intensive-care patients, and their studies involved shorter sedation periods (48 h and 72 h). Our results are in keeping with the values reported by these authors as regards the mean terminal half-life and total volume of distribution [4, 15] Total clearance values were also similar in the three studies in accordance with values obtained in anesthesia after a bolus or short infusion [5, 6, 7].

In 1992 Hughes et al. [16] introduced the concept of a "context-sensitive half-time," the time required for a 50% decrease in the plasma concentration, which is thought to be a more clinically relevant measure of drug decay than is the terminal half-life. Indeed, Kapila et al. [17] measured a 50% decrease in remifentanil and alfentanil concentration after a 3 h infusion and compared it with the computer-modeled context-sensitive half-time. The 50% decrease in drug concentration after the end of administration was more predicted by the context-sensitive half-time than by the elimination half-life. By computer simulations of sufentanil decay Shafer et al [18]. calculated that a 50% decrease in the effect-site concentration would take 0.8 h after a 10 h infusion. In our study after a mean administration time of 12 days we observed a short α distribution phase, with $t_{1/2\alpha}$=1.33 h. Although this parameter cannot be considered mathematically as the context-sensitive half-time (the "context" here is the duration of a constant infusion), this rapid decay phase shortens the period required for a 50% decrement time in the sufentanil concentration ($tcp_{0/2}$=4.7± 3.7 h) even after a long infusion period (18–23 days). This confirms that the calculated $t_{1/2\alpha}$ and the measured $tcp_{0/2}$ are in close agreement with the context-sensitive half-times. The calculated $t_{1/2\alpha}$ might thus be a more relevant indicator of drug decay after lengthy infusion than is the terminal half-life, and it may also be a more faithful indicator of the clinical reversibility of sedation. Nevertheless, it must be kept in mind that pharmacokinetic parameters describe only volumes or drug concentration decrements and do not predict reliably the pharmacodynamic effect [19].

The sedation regimen in this study was analgesia/opiate-based, with the difficulty of separating the clinical effects of analgesia and sedation in intubated patients. Midazolam is often chosen in combination because of its short half-life, but benzodiazepine tolerance has been reported after long-term administration. The increase in the daily midazolam dose may lead to drug accumulation, prolonged recovery times, and delayed weaning from the ventilator [1]. Moreover, midazolam pharmacokinetics are markedly altered in critically ill patients and can lead to unwanted cumulative sedative effects [20]. The goal of sedation in ICU is now to keep the patient comfortable but easily aroused (Ramsay score 2 or 3) rather than to be deeply comatose. This is the reason why the infusion of sedatives with large dose of benzodiazepines and/or narcotics have been abandoned. The balanced combination of analgesics and sedative drugs, eliminated rapidly and nonaccumulating, with effective and titratable analgesic/sedative therapeutic regimen tailored to individual needs, is now favored. Sufentanil, because of its hypnotic potency greater than other opiates [9] and under pharmacokinetic considerations, appears to fulfill the criteria of good agent for sedation.

Remifentanil is a new short-acting μ-receptor opioid and is now licensed for ICU use. Remifentanil differs from other phenylpiperidines by its pharmacokinetic profile and its extrahepatic metabolism by blood and tissue nonspecific esterases. The time required for decrease in plasmatic concentrations is then very short and seems to be independent of infusion duration [21]. It has been shown that remifentanil can be used as the sole drug since a good level of sedation is obtained [22]. Recently Soltész et al. [23] investigated the analgesic effect and recovery time after the administration of remifentanil in 20 ventilated patients randomized to receive either remifentanil/propofol or sufentanil/propfol sedation. After infusion withdrawal the incidence of spontaneous ventilation was 56% within 10 min in the remifentanil group and 53% within 30 min in the sufentanil group. On the other hand, six patients in the remifentanil group complained of pain vs. none in the sufentanil group, and pa-

tients in the remifentanil group required significantly more propofol that patients in the sufentanil group. In ICU, except for situations requiring neurological assessment by clinical examination, we believe that there is no particular advantage from analgesia and sedation within a few minutes.

In conclusion, during prolonged sufentanil infusion an increased total volume of distribution was observed, leading to an increased terminal half-life $t_{1/2\beta}$. However, total clearance remained stable, in contrast to the case with anesthetic use. Most importantly we observed a rapid distribution phase and a short estimated time required for a 50% decrease in plasma concentrations, leading to low plasma concentrations rapidly after cessation of the infusion. Given the small number of patients involved in this study these results cannot be directly extrapolated to the general population of ICU patients. Further studies are needed to confirm our pharmacokinetic findings and to evaluate their clinical relevance, particularly as regards with weaning and extubation.

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