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Pharmacokinetics and pharmacodynamics of propofol/alfentanil infusions for sedation in ICU patients

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Abstract *Objective:* Population pharmacokinetic analysis and pharmacodynamic profile of propofol/alfentanil infusions for sedation and analgesia of intensive care unit patients for up to 24 h.
Design: Institutional Review Board-approved prospective clinical trial.
Setting: The ten-bed intensive care unit of an university hospital.
Patients: 18 consecutive patients (ten men/eight women; age: 17–73 years, mean 51.6 ± 16.7 years, SD; body weight: 60–110 kg, mean 82.9 ± 11.2 kg, SD) requiring mechanical ventilation and prolonged sedation/analgesia after major surgery or trauma.
Interventions: Plasma propofol and alfentanil concentrations were measured at regular intervals during the long-term drug infusion using a high-performance liquid chromatography (propofol) and radioimmunoassay (alfentanil) analysis. The depth of sedation was controlled by monitoring a two-lead online EEG. Thus, drug application was computer controlled via a closed-loop EEG median-frequency feedback system.
Results: ICU long-term infusion population pharmacokinetics (open three-compartment model) revealed for propofol: central compartment distribution volume (V_1): 31.2 ± 5.3 l; steady-state distribution volume (V_{dss}): 499 ± 173 l; total clearance (Cl_{tot}): 1001– ± 150 ml/min; redistribution half-life ($t_{1/2}\gamma$): 90 ± 23 min; elimination half-life ($t_{1/2}\beta$): 558 ± 218 minutes. For alfentanil: V_1: 31.9 ± 10.1 l; V_{dss}: 124 ± 41 l; Cl_{tot}: 345 ± 70 ml/min; $t_{1/2}\gamma$: 36 ± 15 min; $t_{1/2}\beta$: 275 ± 94 min, respectively.
Conclusions: The population pharmacokinetic analysis of propofol/alfentanil for ICU sedation therapy revealed increased volumes of drug distribution and decreased elimination characteristics as compared to pharmacokinetic data from short-term infusions in surgical patients. This can be attributed in part to altered distribution/redistribution processes and/or drug elimination under the condition of ICU therapy. No significant drug accumulation was observed. For future long-term sedation and analgesia of ICU

patients with propofol/alfentanil, this altered pharmacokinetic behaviour should be taken into consideration to allow a more individualized and safer dosing of this drug combination.

Key words: Intensive care · Sedation · Anaesthetics, intravenous · Propofol · Analgesia · Alfentanil · Pharmacokinetics · Pharmacodynamics

Introduction

Critically ill and mechanically ventilated ICU patients often require prolonged sedation and adequate analgesia. The therapeutic approach should permit an individualized titratable depth of sedation and analgesia, allowing for a rapid reversibility of the sedative state in order to assess the patient's neurologic status and ensure early weaning from artificial ventilation [1]. For this purpose, a combination of sedative and analgesic drugs that is rapidly eliminated and non-cumulating is favoured.

At present, an opiate-benzodiazepine combination is most commonly employed [2], although there is evidence that continuous infusions of midazolam for sedation of ICU patients may lead to accumulation and prolonged recovery [3, 4].

Propofol, a new short-acting anaesthetic drug, is in use for both induction [5] and maintenance of general anaesthesia [6, 7]. This hypnotic agent exhibits a favourable pharmacokinetic profile with a high total-body clearance, a relatively short elimination half-life and a virtual lack of cumulation [7]. Pharmacokinetics have been shown to be unaltered by renal or liver dysfunction [8, 9]. This agent has already been utilized successfully for short- and long-term sedation of ICU patients [10, 11]. For the opioid alfentanil, a short elimination process has also been demonstrated [12], making the combination of these two agents the obvious choice for a titratable and effective analgesic/sedative therapeutic regimen.

So far, only limited pharmacokinetic data are available for this indication range. Thus, altered pharmacokinetics, cumulation and/or drug interactions during continuous long-term administrations especially in an ICU patient population, cannot be ruled out. In order to avoid drug accumulation with undesired side effects and/or unnecessary long recovery periods, a detailed knowledge about the pharmacokinetic and pharmacodynamic drug profile is mandatory. Therefore, in this investigation the pharmacokinetic and pharmacodynamic profile of propofol and alfentanil infusions for sedation of ICU patients for up to 24 h was evaluated.

Methods

Patients

After Institutional Review Board approval, informed consent was obtained from 18 patients (10 men/8 women; age: 17–73 years, mean 51.6 ± 16.7 years, SD; body weight: 60–110 kg, mean 82.9 ± 11.2 kg, SD), who were included in the study: 10 required mechanical ventilation after a major surgical procedure, and 8 were being artificially ventilated and sedated after a major trauma.

All patients were artificially ventilated using a Servo C 900 (Siemens, Germany) ventilator with a pressure-controlled ventilation regimen, maintaining the P_aO_2 at an average of 151 ± 16 mmHg and the P_aCO_2 at a mean value of 32 ± 1 mmHg (mean ± SEM, $n = 18$ patients). It was ascertained that no patient included in the study had compromised liver and/or renal function. Metabolic parameters including urinary output, gastric pH and core temperature were kept within normal limits. Biochemical and haematological blood variables were controlled the day before, during, and the day after cessation of the propofol/alfentanil infusions and showed no statistically significant abnormalities or differences. For each individual patient, an APACHE II score was calculated [13] immediately before the start of the sedative therapy to quantify the severity of illness (Table 1).

Study design

In this study, a completely new approach of drug dosing individualized to each patient's needs was introduced. Sedation was induced and maintained using a continuous infusion of propofol controlled by an EEG median-feedback closed-loop system, which has been demonstrated and used before during general anaesthesia [14, 15]. This system maintained the patients in a state tolerating mechanical ventilation, corresponding clinically to 3–4 on a sedation scale of 1–5 (1: asleep, not arousable, to 5: fully awake and orientated) modified from Ramsey et al. [16]. The median frequency of the patient's EEG power spectrum was obtained and used as the electrophysiologic and quantifiable correlate of depth of sedation [17, 18]. The correlating EEG median frequency was used as the relevant biosignal and input function for a computer-based, closed-loop feedback system for the application of propofol. Thus, propofol concentrations were altered in order to maintain the EEG median frequency at a value of 3–4 Hz.

Alfentanil as the analgesic drug was controlled in an open-loop system using a pharmacokinetic model to achieve predicted serum concentrations in the range of 50–150 ng/ml and adjusted to the patients' analgesic needs measured by clinical haemodynamic and vegetative criteria. Whenever it was possible to communicate with a patient during the sedative and analgesic therapy, he or she was asked about discomfort or pain and the alfentanil infusion was adjusted accordingly. In patients in a deeper state of sedation, other possible reasons for variations in these parameters (e.g., hypovolaemia, shock, considerable doses of vasoactive and sympathomimetic drugs) were ruled out first, followed by close

Table 1 Characteristics of study patients (diagnosis, APACHE II score on admission, total sedation time, number of blood samples drawn for the pharmacokinetic analysis)

Patient no.	Diagnosis	Apache II	Sedation time	Number of blood samples
1	Multiple injuries, including head	24	24 h	5
2	Thoracic empyema	14	20 h	5
3	Carcinoma of the antrum	16	15 h	6
4	Pheumonia	24	13 h	5
5	Acute pancreatitis	25	21 h	8
6	Carcinoma of the pancreas	14	22 h	10
7	Abdominal aortic aneurysm	18	18 h	6
8	Multiple injuries	22	21 h	7
9	Carcinoma of the lung	23	21 h	6
10	Abdominal aortic aneurysm	18	15 h	5
11	Multiple injuries, including head	24	24 h	8
12	Pancreatitis, pleural effusion	15	22 h	7
13	Multiple injuries	16	23 h	9
14	Carcinoma of the oesophagus	21	21 h	5
15	Craniofacial carcinoma	15	15 h	6
16	Multiple injuries, including head	25	24 h	9
17	Multiple injuries, including head	15	10 h	4
18	Multiple injuries	21	21 h	7
Range		15–25	10–24 h	4–10
Mean ± SD		19 ± 4	19.4 ± 4.2 h	6.6 ± 1.6

observation of the particular patient. Observation of a combination of all criteria (increased heart rate plus increased blood pressure and clear signs of increased sweating) was considered as indicating inadequate analgesic therapy and the alfentanil infusion was correspondingly increased until cessation of the described symptoms.

Propofol and alfentanil assay

Blood samples for the measurement of propofol and alfentanil concentrations were taken from the patient's arterial catheter for a blank assay before the start and at appropriate 2-h time intervals during the infusion (see Table 1). After gentle shaking of the tube, each sample (5 ml) was immediately stored at 4 °C until further analysis.

Propofol concentrations were measured in whole blood samples by a high-pressure liquid chromatography (HPLC-ECT), as published before [19] but with the modification of electrochemical detection. Alfentanil blood levels were determined by a radioimmune assay (RIA) as reported elsewhere [20].

Data analysis

The acquired plasma concentration data were analysed utilizing the NONMEM program (Version III, double precision), adjusted for a population pharmacokinetic analysis [21, 22]. NONMEM allows simultaneous non-linear regression of population data, which means that not only the average pharmacokinetic parameters of the population can be estimated, but also their inter- and intraindividual variability. A further advantage of this approach is that the number of samples per individual can be kept relatively small (see Table 1). In addition, it is possible to investigate the influence of such covariates as age, weight or gender.

Pharmacokinetic model

A three-compartment open-body model with elimination from the central compartment was used. The pharmacokinetic model assumed that propofol and alfentanil pharmacokinetics are first order and concentration independent. Preliminary analysis of propofol and alfentanil [12] comparing two- and three-compartment models showed that a three-compartment model is superior for an extended period of observation, as in our case. As fit parameters we chose the central volume of distribution (Vc), the total body clearance (Cl) and the microconstants k12, k21, k13 and k31, which describe the transfer between the compartments. The closed-form solution for the plasma concentration [c(t)] at time t with an infusion rate $I(t)$ is given by the following formulas:

$$g(t) = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + C \cdot e^{-\gamma t} \tag{1}$$

$$C(t) = \int_0^t g(t - t') \cdot I(t')\, dt' \tag{2}$$

The macroconstants A, B, C, α, β, γ were calculated from the microconstants to determine the plasma concentration. Interindividual variability, i.e. difference in the plasma concentration profile among different patients, can be described by including random effects into the regression model, allowing some parameters to vary randomly among patients. We assumed interindividual differences for the Vc and for Cl. Based on our own previous experience and other reports [12], we used the "constant coefficient of variation" model. This means that for the i-th individual:

$$Cl_i = Cl \cdot (1 + \eta_i^{(Cl)}) \quad E(\eta_i^{(Cl)}) = 0 \quad Var(\eta_i^{(Cl)}) = \sigma_{Cl}^2 \tag{3}$$

$$V_{c_i} = V_c \cdot (1 + \eta_i^{(V_c)}) \quad E(\eta_i^{(V_c)}) = 0 \quad Var(\eta_i^{(V_c)}) = \sigma_{V_c}^2 \tag{4}$$

where Cl and V_c are the mean population values of the parameters.

For the remaining intraindividual variability, which is due to assay errors, time inaccuracy, model misspecification, etc, we used an analogous model:

$$C_{ij} = C_{pij} \cdot (1 + \varepsilon_{ij}) \quad E(\varepsilon_{ij}) = 0 \quad Var(\varepsilon_{ij}) = \sigma_\varepsilon^2 \tag{5}$$

where c_{ij} is the j-th measured plasma concentration of the i-th individual and c_{pij} is the corresponding predicted concentration [calculated from Eq. (2)]. By using this proportional model for the residual error, one assumes that the error between the observed and

predicted observations increases with the predicted concentration, a phenomenon frequently observed with pharmacokinetic data [12].

NONMEM estimates the mean population values of the pharmacokinetic fit parameters, the interindividual variances σ^2_{Cl} and $\sigma^2_{V_c}$ and the intraindividual variance σ^2_ε, as well as the standard errors (SEM) of all parameters.

Goodness of fit was tested using residual plots and the "objective function", which is supported by NONMEM output and which is asymptotically χ^2 distributed.

Results

All 18 patients could be sedated successfully with the EEG median-feedback closed-loop system, on average for 19 ± 4 h (10–24 h). No patient demonstrated significant blood chemistry or haematologic abnormalities that could be attributed to the sedative/analgesic therapeutic regimen. According to a precalculated infusion scheme based on a population pharmacokinetic analysis of surgical patients [6, 7], our intensive care patients received propofol via an automated, closed-loop feedback, computer-controlled infusion. The infusion rate was adjusted to the patient's specific clinical needs. The aim of our investigation was to maintain a patient in a state of light sedation while tolerating mechanical ventilation. This clinical sedation level corresponded to an EEG median frequency of 1.5–3.5 Hz, although a range of variability in this heterogenous group of ICU patients has to be acknowledged.

In order to demonstrate the pharmacodynamic profile of our sedative therapy, a typical and representative case is shown in Fig. 1.

In this figure, the 15-h sedation period of a 56-year-old female patient who underwent a major abdominal surgical procedure including a complete gastrectomy with revision of the pancreatic duct is shown. The upper panel shows the time course of the EEG median frequency as the electrophysiologic correlate of the depth of sedation; the lower panel combines the information about the computer-controlled and-dosed propofol infusion rates with the resulting calculated and measured propofol serum levels. Upon admission to the ICU immediately after surgery, we evaluated an almost awake patient with corresponding EEG median frequencies between 6 and 10 Hz. After a rapid computer-controlled propofol bolus infusion the EEG median frequency decreased to a level between 2 and 4 Hz and clinical assessment revealed a sleepy patient with slow reactions on light physical contact.

This EEG median frequency of 4 Hz was used as the target input biosignal for the computer-controlled, closed-loop propofol infusion. Thus, the patient was kept at this level of sedation for the remaining time course. An intact day-and-night sleep rhythm may be suggested by a reduced EEG median frequency sleep pattern and a resulting significantly reduced sedative drug demand between 1:00 am and 6:00 am. With the start of the regular ICU day routine at 6:00 am, the patient became more vigilant with a higher EEG median frequency followed by an increased computer-controlled application of propofol. The analgesic drug therapy was adjusted to the patient's needs according to vegetative (sweating, etc.) and/or haemodynamic (tachycardia, hypertension, etc.) criteria and were aimed at alfentanil serum concentrations between 50 and 150 ng/ml.

Average propofol infusion rates of between 1.0 and 3.5 $mg \cdot kg^{-1} h^{-1}$ were applied by the computer-controlled pump device and aimed at predicted plasma

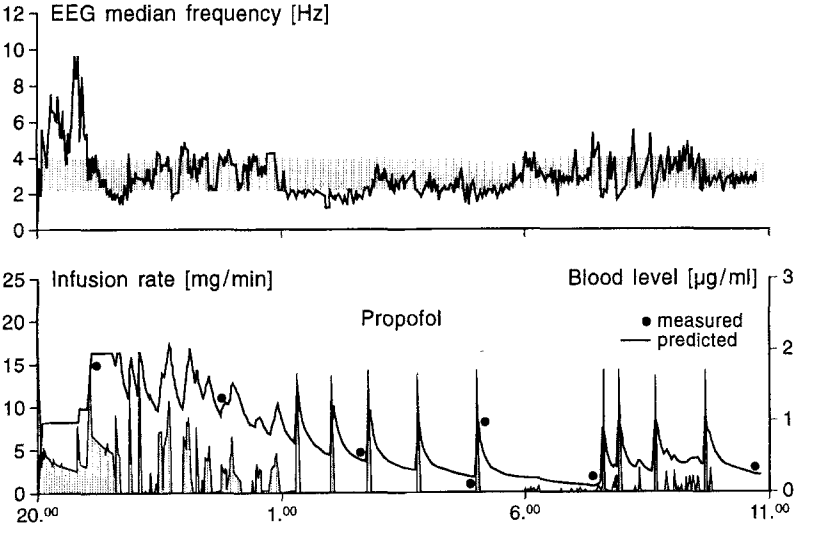

Fig. 1 Time course of sedation in a representative patient (56 years, female, major abdominal surgery: total gastrectomy, pancreatic duct revision) over 15 h. *Upper panel*: on-line mean EEG median frequency (Hz). *Lower panel*: calculated predicted (*solid line*) and measured (*filled dots*) propofol serum concentrations (µg/ml); computer-controlled propofol infusion rates are depicted as *filled bars* at the *bottom* of the *lower panel* (mg/min)

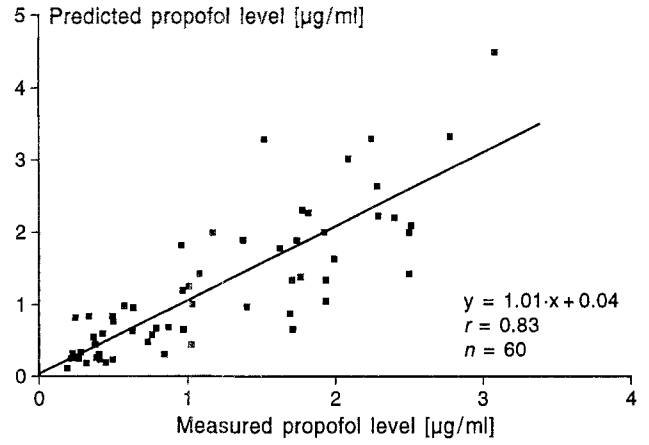

Fig. 2 Regression analysis of the predicted versus measured propofol serum concentration

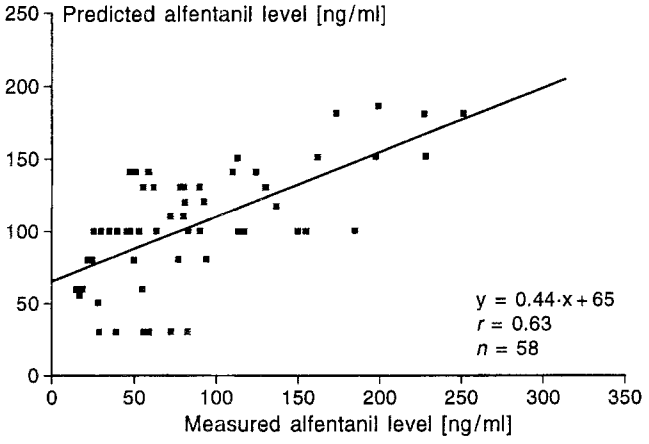

Fig. 3 Regression analysis of the predicted versus measured alfentanil serum concentration

concentrations of between 0.5 and 2.0 µg/ml to keep our patients at EEG median frequency levels between 2 and 4 Hz. A sufficient analgesic therapy was reached on average by alfentanil infusion rates between 0.02 and 0.04 $mg \cdot kg^{-1} \cdot h^{-1}$ with corresponding predicted plasma levels between 0.05 and 0.15 µg/ml.

Figures 2 and 3 demonstrate the relationship between the combined predicted and measured plasma concentrations for propofol (Fig. 2) and alfentanil (Fig. 3) for all 18 study patients. A total of 118 measured serum concentrations were compared with the predicted serum concentrations as derived from pharmacokinetics based on investigations on volunteers and ASA I-II general surgery patients [6, 7, 14]. After a regression analysis was performed for this data, the following relationship between predicted and measured serum concentrations became evident: the regression coefficient for measured versus predicted serum propofol concentrations was 0.83. The alfentanil data could be regressed with a regression coefficient of 0.63.

Although individual patients demonstrates a significant degree of variability, the overall regression analysis shows a close relationship between the measured and calculated drug concentrations, indicating the validity of the chosen pharmacokinetic model parameters.

The population pharmacokinetic analysis of the data (for details see Methods) and the resulting derived pharmacokinetic parameters, including apparent volume of distribution of the central compartment (V_1) and at steady state (V_{dss}), total clearance (Cl_{tot}), redistribution half-life ($t_{1/2}\gamma$) and elimination half-life ($t_{1/2}\beta$), are presented in Table 2.

Discussion

Propofol is widely used for induction [5] and maintenance [6, 7] of general anaesthesia. Recently, propofol long-term infusions have been applied to ICU patients to ensure adequate and safe sedation during ICU therapy [10, 11, 23]. So far, all patients were sedated after a surgical intervention according to a clinical sedation score with an initial propofol bolus and a successive infusion with fixed infusion rates averaging between 1.93 [23] and 2.85 mg/kgBW/h without supportive analgesic therapy [10] and 0.73 mg/kgBW/h with an alfentanil infusion of 0.3 mg/kgBW/h [11]. From these initial studies, only limited detailed pharmacokinetic data for long-term use in critically ill patients are available (see Tables 3 and 4).

Table 2 Summarized pharmacokinetic parameters (mean ± SEM) of propofol and alfentanil in (open three-compartment model with 18 patients each and 118 data points (Cl_{tot} total clearance, $t_{1/2}\gamma$ redistribution half-life, $t_{a/2}\beta$ elimination half-life V_1 central compartment volume, V_{dss} volume of distribution in steady state

Pharmacokinetic parameter	V_1 (l)	V_{dss} (l)	Cl_{tot} (ml/min)	$t_{1/2}\gamma$ (min)	$t_{1/2}\beta$ (min)
Propofol	31.2 ± 5.3	499 ± 173	1001 ± 150	90.5 ± 23	558 ± 218
Alfentanil	31.9 ± 10.1	124 ± 41	345 ± 70	36 ± 15	275 ± 94

Table 3 Summarized pharmacokinetic parameters (mean ± SEM) for propofol (this study and data from the literature)

Study design	ICU sedation	ICU sedation	ICU sedation	Anaesthesia	Anaesthesia	Anaesthesia	Anaesthesia
Reference	This study	[25]	[26]	[7]	[27]	[9]	[28]
Duration (h)	Infusion, 24 h	Infusion, 72 h	Infusion, 17 h	Infusion, 3 h	Infusion, 2 h	Bolus	Bolus, infusion
No. of patients	18	9	10	20	18	10	85
Pharmacokinetic model (no. of compartments)	Open (3)	None	Open (2)	Open (3)	Open (3)	Open (3)	Open (3)
V_1 (l)	31.2 ± 5.3	–[a]	–[a]	8 ± 5	17 ± 7	20.6 ± 17	18.9 ± 3.5
V_{dss} (l)	499 ± 173	1666 ± 756	–[a]	224 ± 129	287 ± 212	384 ± 222	249 ± 75
Cl_{tot} (ml/min)	1001 ± 150	1570 ± 560	1140 ± 160	1960 ± 570	1770 ± 322	2300 ± 610	1540 ± 140
$t_{1/2}\gamma$ (min)	90.5 ± 23	–[a]	13 ± 2	30 ± 16	31 ± 15	30 ± 20	30 ± 10
$t_{1/2}\beta$ (min)	558 ± 218	1878 ± 672	470 ± 61	232 ± 165	355 ± 227	246 ± 123	232 ± 89

[a] Data not available

The aim of this study was the detailed analysis of the population pharmacokinetic and -dynamic profile of propofol and alfentanil when administered by computer-controlled infusions to ICU patients for up to 24 h. For the first time, patients could be sedated successfully in the clinical ICU routine by a computer-controlled, closed-loop feed-back infusion of propofol based on the patients' EEG median frequency. Nevertheless, future studies will have to evaluate possible limitations of this therapeutic approach, such as recordings of pathological EEGs of ICU patients with severe neurological diseases, including head trauma.

During general anaesthesia attained with a total intravenous technique with propofol and alfentanil, average propofol blood levels of 2.42 μg/ml (± 0.43; SD) were required for adequate anaesthesia and average alfentanil levels of 0.29 μg/ml (± 0.07; SD) ensured sufficient analgesia during major noxious stimulation [24]. To achieve the therapeutic goal of this study, i.e. ensuring a sedated patient tolerating mechanical ventilation with no distress, lower blood levels of propofol and alfentanil were expected and achieved.

The computer software used for calculation of the predicted drug plasma levels and for selection of the infusion rates was based on population pharmacokinetic data from short-term general anaesthesia in surgical patients [6, 7, 12, 14]. In our heterogeneous group of ICU patients with a long-term sedative/analgesic drug application, a different pharmacokinetic drug profile was expected.

The population pharmacokinetic analysis was based on an open three- compartment model for the best data fit. Our analysis for propofol yielded a central distribution volume of 31.2 l, a steady-state distribution volume of 499 l, a total clearance of 1001 ml/min, a redistribution half-life of 90 min and an elimination half-life of 558 min (see Table 2).

Other investigations on propofol long-term sedation pharmacokinetics included the data from 9 [25] and 10 ICU patients [26]. Albanese et al. [25] estimated a significantly (factor 3) larger steady-state distribution volume and elimination half-life than we recorded and McMurry et al. [26] calculated a comparable total clearance and elimination half-life but a much shorter redistribution half-life (Table 3), partly because different pharmacokinetic models were used.

The pharmacokinetic analysis of data from volunteer or general surgery patient studies with propofol administration as intravenous boluses [9, 28] or short-term infusion [7, 27] reveals a different behaviour. Comparison of these data with the pharmacokinetic analysis of the ICU patient population, showed that the latter patient group distribution volumes are

significantly larger and the elimination is significantly decreased (Table 3) by a smaller total clearance rate. This can be explained in part by changes in organ perfusion resulting in reduced liver blood flows. In addition, propofol was distributed into deep lipophilic tissue compartments (increased central compartment and steady-state distribution volume) owing to changes in body composition.

The regression analysis of the predicted and measured propofol plasma levels did not reach the line of identity (measured concentration = predicted concentration) but revealed a close relation for propofol with a regression coefficient of 0.83 and a fair assumption of the slope (1.01) and offset (0.04 μg/ml) (Fig. 2), despite considerable variability in individual measured versus predicted serum concentrations.

Interestingly, the altered pharmacokinetic behaviour of propofol in this study did not lead to a significant disproportion between the predicted and measured propofol serum levels, although the computer-controlled infusion was based on the pharmacokinetic parameters of otherwise healthy surgical patients [28]. Probably the effects observed in this study (increased distribution volumes and decreased total clearance rate) compensate each other, resulting in this surprisingly good correlation of predicted and measured serum levels.

The population pharmacokinetic analysis for alfentanil revealed a comparable trend (Table 4). Maitre et al. performed a population pharmacokinetic analysis of 48 otherwise healthy patients [12] who had received either an alfentanil bolus or a short infusion for a short surgical intervention. Compared with our data (Table 2), Maitre et al. calculated a much smaller central distribution volume (8.2 ± 1.5 l vs. ICU 31.9 ± 10.1 l) and steady-state distribution volume (33 ± 10 l vs. ICU 124 ± 41 l) and a decreased elimination half-life (97 ± 26 min vs. ICU 275 ± 94 min) than we did confirming the slower elimination process of our ICU patient population for alfentanil also (for comparison, see Table 4).

A wide range of interindividual pharmacokinetic variability for alfentanil has been demonstrated before [12] and may also be identified in our data. In contrast to the regression analysis of propofol, the regression analysis of the measured versus the predicted alfentanil blood levels reveals a poor value for the correlation coefficient ($r = 0.63$) as well as for the assumption of the slope (0.44) and offset (65.0 ng/ml) (Fig. 3), indicating a wide spread of individual data points.

These altered alfentanil pharmacokinetics in our patient population may be attributed in part to changes in protein binding and/or regional blood flow affecting tissue distribution and redistribution, hepatic clearance and enzyme-modulated elimination processes. Recently it has been shown that the human liver microsomal cytochrome P-450 3A4 contributes significantly to alfentanil oxidation and metabolism [30]. Thus, we cannot rule out the possibility of pharmacokinetic interactions between alfentanil and other concomitantly administered drugs that are also substrates for, or inducers of, cytochrome P-450 3A4 in our intensive care patients. Furthermore, a pharmacogenetic modulation of alfentanil action cannot be ruled out, perhaps due to the considerable heterogeneity in alfentanil metabolism caused by differences in cytochrome P-450 3A4 activity.

In conclusion, the population pharmacokinetic analysis of longer-lasting infusions of propofol and alfentanil for the sedation and analgesia of an ICU patient population revealed increased volumes of drug distribution and decreased elimination characteristics compared with pharmacokinetic data from surgical patients. This decreased elimination process can be attributed in part to altered distribution/redistribution processes and/or drug metabolism. The high-clearance drug propofol is most affected by changes in liver blood flow compared with the low-clearance drug

Table 4 Summarized pharmacokinetic parameters (mean ± SEM) for alfentanial (this study and data from the literature)

Study design	ICU analgesia	Anaesthesia	Anaesthesia	Anaesthesia
Reference	This study	[29]	[29]	[12]
Duration (hours)	Infusion, 24 h	Infusion, 2 h	Infusion, 3 h	Infusion, 3 h
No. of patients	18	11	7	48
Pharmacokinetic model (no. of compartments)	Open 3	Open 2	Open 2	Open 3
V (l)	31.9 ± 10.1	9 ± 2	10 ± 6	8 ± 5
V_{dss} (l)	124 ± 41	26 ± 7	30 ± 23	33 ± 10
Cl_{tot} (ml/min)	345 ± 70	275 ± 51	368 ± 105	356 ± 87
t (min)	36 ± 15	–[a]	–[a]	30 ± 12
t (min)	275 ± 94	84 ± 26	69 ± 43	97 ± 26

[a] Data not available

alfentanil, with its predominantly enzyme-limited elimination. A considerable accumulation of both pharmacologic agents during long-term infusions did not occur in this study and has not been reported in the literature so far.

For future long-term sedation and analgesia of ICU patients with propofol/alfentanil, this altered pharmacokinetic behaviour should lead to a more individualized and safer application of this drug combination. Eventually, future long-term, closed-loop feedback propofol/alfentanil applications will require modified pharmacokinetic parameters adjusted according to the results of this population pharmacokinetic analysis. In addition, close pharmacodynamic monitoring with online monitoring of the EEG median frequency allows for an effective drug dosing, avoiding the unnecessary side effects drug over- or underdosing.

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