Propofol Alters the Pharmacokinetics of Alfentanil in Healthy Male Volunteers

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Background: The influence of propofol on the pharmacokinetics of alfentanil is poorly understood. The authors therefore studied the effect of a pseudo–steady state concentration of propofol on the pharmacokinetics of alfentanil.

Methods: The pharmacokinetics of alfentanil was studied on two occasions in eight male volunteers in a randomized crossover manner with a 3-week interval. While breathing 30% O_2 in air, 12.5 µg/kg intravenous alfentanil was given in 2 min, followed by 25 µg · kg^{-1} · h^{-1} for 58 min (sessions A and B). During session B, a target controlled infusion of propofol (target concentration, 1.5 µg/ml) was given from 10 min before the start until 6 h after termination of the alfentanil infusion. Blood pressure, cardiac output, electrocardiogram, respiratory rate, oxygen saturation, and end-tidal carbon dioxide were monitored. Venous blood samples for determination of the plasma alfentanil concentration were collected until 6 h after termination of the alfentanil infusion. Nonlinear mixed-effects population pharmacokinetic models examining the influence of propofol and mean arterial pressure were constructed.

Results: A three-compartment model, including a lag time accounting for the venous blood sampling, adequately described the concentration–time curves of alfentanil. Propofol decreased the elimination clearance of alfentanil by 15%, rapid distribution clearance by 68%, slow distribution clearance by 51%, and lag time by 62%. Mean arterial pressure and systemic vascular resistance were significantly lower in the presence of propofol. Scaling the pharmacokinetic parameters to the mean arterial pressure instead of propofol improved the model.

Conclusions: Propofol alters the pharmacokinetics of alfentanil. Hemodynamic changes induced by propofol may have an important influence on the pharmacokinetics of alfentanil.

IN anesthetic practice, alfentanil is frequently combined with propofol to provide total intravenous anesthesia for surgical procedures. The pharmacokinetics of propofol and alfentanil, in the absence of other drugs, have been described by several investigators and for various patient populations.[1,2] More recently, the pharmacodynamic interaction between propofol and alfentanil has been reported.[3] These studies demonstrated that propofol reduces alfentanil requirements for suppression of responses to several clinically relevant stimuli. The pharmacokinetic interaction between propofol and alfentanil, however, has not been determined, although the possibility of such an interaction has been suggested in previous studies. Both Gepts *et al.*[4] and Pavlin *et al.*[5] reported that plasma alfentanil concentrations in the presence of propofol were higher than in the absence of propofol. The mechanism of the interaction, its precise magnitude, and its clinical relevance has not been determined. We therefore studied the pharmacokinetics of alfentanil when given as sole agent and in the presence of a pseudo–steady state blood concentration of propofol in eight healthy male volunteers. In addition, changes in hemodynamic parameters during and after the alfentanil infusion were studied in the presence and absence of propofol. Nonlinear mixed-effects population pharmacokinetic models examining the influence of propofol and mean arterial pressure on alfentanil pharmacokinetics were constructed.

Materials and Methods

Volunteers and Study Protocol

After obtaining approval from the Leiden University Medical Center Medical Ethics Committee and informed consent, eight healthy male volunteers, aged 20–30 yr, participated in the study. The volunteers were within 30% of the ideal body weight, had no history of hepatic or renal disease, and did not take any prescription drugs in the month before and during the course of the investigation. They denied consumption of more than 20 g of alcohol or smoking more than 10 cigarettes per day.

The volunteers were studied on two separate occasions according to a randomized two-way crossover design. On one occasion, they received a bolus dose of 12.5 µg/kg alfentanil in 2 min, followed by an infusion of 25 µg · kg^{-1} · h^{-1} for 58 min (control, session A). On the other occasion, they received the same regimen of alfentanil in the presence of a target controlled propofol infusion (target propofol concentration, 1.5 µg/ml), which was started 10 min before the start of and was maintained until 6 h after the termination of the alfentanil infusion (session B). The order of the two sessions was randomized, such that in half of the volunteers the control session preceded the other session and *vice versa*. The study sessions were separated by a 3-week interval.

Volunteers fasted from midnight on the night before the study until the last blood sample had been collected. During the administration of alfentanil, they breathed 30% oxygen in air. When indicated, ventilation was as-

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sisted using a face mask to maintain the end-tidal partial pressure less than 6.5 kPa (49 mmHg). After termination of a session, the subjects received a light meal and were monitored for another 4 h before they were allowed to leave the hospital.

Materials

An intravenous cannula was inserted into a large forearm vein for the infusion of propofol and alfentanil. Another intravenous cannula was inserted in a large vein of the contralateral arm for the collection of blood samples for determination of the blood propofol and plasma alfentanil concentrations.

Alfentanil was administered with a conventional infusion pump. Prestudy computer simulations of the alfentanil infusion scheme demonstrated that the plasma alfentanil concentration was not likely to exceed 80 ng/ml, allowing spontaneous ventilation. A pocket computer, provided with three-compartment pharmacokinetic data of propofol,[6] was used to control[7] a pilot anesthesia infusion pump for the target controlled infusion of propofol.

Blood pressure and cardiac output were measured noninvasively, and the electrocardiogram, respiratory rate, peripheral oxyhemoglobin saturation, and end-tidal carbon dioxide partial pressure were monitored continuously throughout the study. Cardiac output was measured noninvasively using a thoracic bioimpedance system. Cardiac output measured by this method has been shown to correlate well with cardiac output measured by the conventional thermodilution method ($r^2 = 0.74$).[8] The systemic vascular resistance was calculated from the mean arterial pressure and thoracic electrical bioimpedance-derived cardiac output. The investigators recorded all adverse events.

Blood Samples and Assays

Blank venous blood samples for calibration purposes (20 ml) were obtained before the start of the alfentanil infusion. Additional blood samples (5 ml) for the determination of the plasma alfentanil concentrations were collected in heparinized syringes 2, 3, 5, 10, 20, 30, 45, and 60 min after the start of the alfentanil infusion and 0.5, 1, 2, 3, 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 min after termination of the alfentanil infusion. These samples were centrifuged to obtain plasma that was stored at −20°C until analysis. The concentrations of alfentanil in plasma were determined by capillary gas chromatography.[9] The coefficient of variation of this method was less than or equal to 4% in the concentration range encountered in this study. The limit of detection was 0.8 ng/ml.

During session B, additional blood samples (3 ml) for determination of whole-blood propofol concentrations were collected before, 15, 45, 75, and 120 min after the start of the alfentanil infusion and from then on at hourly intervals until 6 h after termination of the alfentanil

infusion. These samples were transferred into test tubes containing potassium oxalate and stored at 4°C. Propofol concentrations in blood were measured by reversed-phase high-performance liquid chromatography.[10] The coefficient of variation of this method was less than or equal to 3% in the concentration range encountered in this study. The limit of detection was 11.7 ng/ml. Propofol assays were conducted within 12 weeks.

Pharmacokinetic and Statistical Analysis

Data analysis was performed using a three-step approach combining Bayesian regression and NONMEM[11] population analysis as previously described by Maitre *et al.*[12] In the first step, the computer program NONMEM (version V, level 1.1) was used to estimate the population pharmacokinetic parameters in sessions A and B.

Population pharmacokinetic parameters were estimated with NONMEM using the "first order" method for two- (ADVAN3) and three-compartment (ADVAN11) models with and without lag time. For the intraindividual variability, a proportional error model was used. The interindividual variability of each of the model parameters (central volume of distribution [V_1], small peripheral volume of distribution [V_2], large peripheral volume of distribution [V_3], elimination clearance [Cl_1], rapid distribution clearance [Cl_2], slow distribution clearance [Cl_3], except for lag-time) was modeled using a log normal variance model:

$$\Theta_{individual} = \Theta_{typical,k} \cdot e^{\eta_{individual}} \qquad (1)$$

where $\Theta_{individual}$ is the value in the individual (except for lag time), $\Theta_{typical,k}$ is the typical value of the parameter in the population in session k, and $\eta_{individual}$ is a normally distributed random variable with a mean of zero and a variance of ω^2, which is estimated by NONMEM. In the ADVAN routines of NONMEM, the lag time cannot exceed the time between dose changes, in our case 2 min. Preliminary individual analyses yielded lag times less than 2 min. The method to assign interindividual variability to the lag time constraining it to the interval 0–2 min is described in the Appendix. The coefficients of variation were calculated as the square root of the variance of η, and being asymmetric, are only approximately the coefficients of variation as usually defined. The likelihood ratio test was used to assess significance of incorporating lag time and the third compartment. A difference corresponding to $P < 0.05$ was considered significant.

To determine whether the presence of propofol could explain the observed pharmacokinetic changes, a model was constructed in which the presence or absence of propofol was used as a covariate. Initially, all pharmacokinetic parameters were allowed to have a separate typical value (see equation 1) for each of the two sessions. Next, each of the parameters were sequentially constrained to be the same for the two sessions, and the one

yielding the smallest change of the difference between $-2 \times$ log likelihood ($-2LL$, supplied by NONMEM) was kept constrained, until this difference exceeded 3.84 ($P < 0.05$) according to the likelihood ratio test. Finally, to assess the improvement of the model using the covariates, the difference in the $-2LL$ of this final model and the model without covariate was examined to assess total statistical significance. A difference corresponding to $P < 0.05$ was considered significant.

To determine whether a hemodynamic covariate could explain the observed pharmacokinetic changes, a second model was constructed in which hemodynamic covariates were used instead of propofol as covariate. Hemodynamic parameters that were tested in the Bayesian regression were average cardiac output, cardiac index, stroke volume, heart rate, mean arterial blood pressure, and systemic vascular resistance of each volunteer during the 420-min study period. Linear relations between covariates and the Bayesian estimates of the interindividual variability term (η) were examined. The hemodynamic parameters that appeared to affect the individual Bayesian estimates of η were entered into the NONMEM regression model as covariates in a stepwise manner as:

$$\Theta_{individual} = \Theta_{typical,k} \cdot e^{(\eta_{individual} + \alpha \cdot (covariate - median\ of\ covariate))}$$
(2)

Initially, all αs were unconstrained. Next, they were sequentially fixed to zero. The one yielding the smallest change of the difference between $-2LL$ was kept fixed, until this difference exceeded 3.84 ($P < 0.05$) according to the likelihood ratio test. Once an important covariate was identified, it was left in the model, and other covariates were tested in turn against this new model. Finally, to assess the improvement of the model using the covariates, the difference in the $-2LL$ of this final model and the model without covariate was examined to assess total statistical significance.

Analysis of Hemodynamic Data

The arithmetic means of the hemodynamic parameters (cardiac output, cardiac index, stroke volume, heart rate, mean arterial blood pressure, and systemic vascular resistance), as present during the 420-min study period in each volunteer, were calculated and compared between the two sessions by a paired t test.

Furthermore, the arithmetic means of the hemodynamic parameters (cardiac output, cardiac index, stroke volume, heart rate, mean arterial blood pressure, and systemic vascular resistance) as obtained in the time period between the collection of two subsequent alfentanil blood samples were calculated for each volunteer over the 420-min study period. These mean hemodynamic parameter values were used in the GLM repeated-measures procedure of the statistical software program to determine whether these differed between sessions A and B as a result of the addition of propofol, whether these changed significantly as a result of the alfentanil infusion scheme, or whether the hemodynamic change in time was influenced significantly by the addition of propofol.

Computer Simulations

The implications of the pharmacokinetic interaction between propofol and alfentanil were explored using the pharmacokinetic parameters of alfentanil for a 74-kg male in the presence and absence of propofol in computer simulations. Plasma alfentanil concentrations were simulated according to the alfentanil infusion scheme used in this study. The context-sensitive half-time (*i.e.*, the time needed for a plasma concentration to decrease by 50% after termination of a target controlled infusion) of alfentanil in the absence and presence of propofol was calculated for target controlled infusions, with constant target concentration lasting 0–240 min.

Results

All eight volunteers completed the study without adverse events. The mean ($\pm$ SD) age, weight, and height were 24 ± 3 yr, 74 ± 6 kg, and 1.82 ± 0.07 m. A total of 342 blood samples for plasma alfentanil concentration analysis were collected and used in the pharmacokinetic analysis. Figure 1 shows the measured plasma alfentanil concentrations for the first 15 min and the remainder of the study period in the presence and absence of propofol. During the first few minutes after the start of the alfentanil infusion, plasma alfentanil concentrations were 3–10 times higher when given in the presence of propofol than when alfentanil was given alone. During the remainder of the alfentanil infusion and up to 6 h after infusion, plasma alfentanil concentrations tended to be higher as well during session B compared with session A. Whole-blood propofol concentrations were sufficiently stable over time (fig. 2). Mean blood propofol concentrations calculated from all collected blood samples per subject ranged from 0.85 to 1.75 μg/ml in the eight volunteers.

NONMEM Analysis with Propofol as Covariate

The concentration–time profile of alfentanil was adequately described in all subjects in both sessions by a three-compartment model with a lag time (fig. 3). The results of this analysis are presented in table 1. The table provides estimates of the population pharmacokinetic parameters for alfentanil with the presence or absence of propofol incorporated into the model as covariate. The NONMEM analysis determined the presence or absence of propofol as a significant covariate of Cl_1, Cl_2, and Cl_3. The difference in $-2LL$ between the final model and the model without the covariates was 52, which corresponds to $P < 0.0001$.
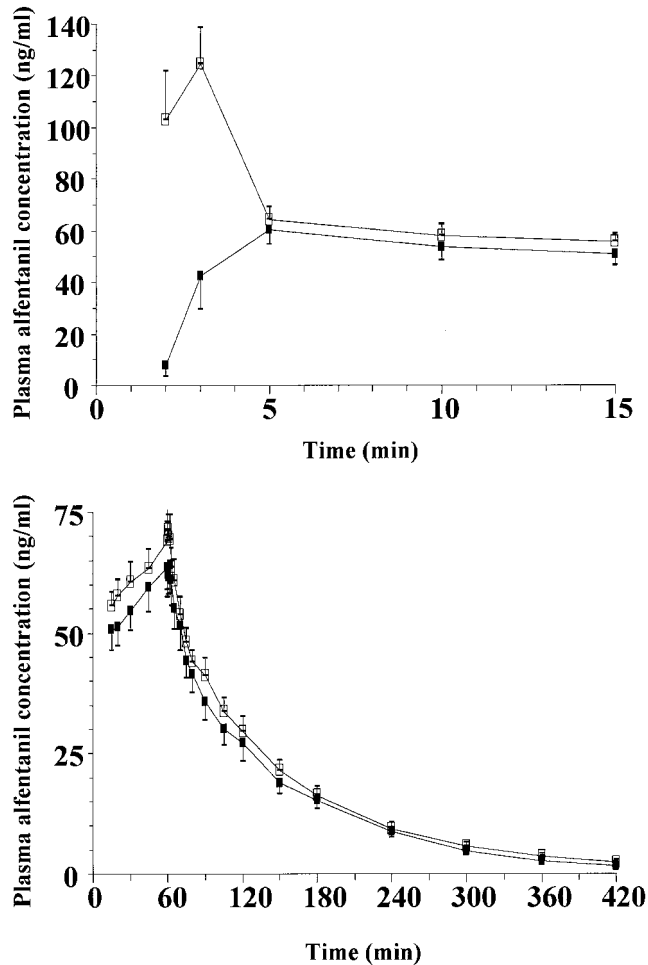
Fig. 1. The mean (± SE) plasma alfentanil concentration *versus* time data in the presence (open squares) and absence (closed squares) of propofol. (*Top*) The first 15 min are shown. (*Bottom*) The remainder of experiment.

NONMEM Analysis with Hemodynamic Parameters as Covariate

From the six Bayesian regression analyses performed, individual pharmacokinetic parameter sets were obtained and plotted against the hemodynamic factors (seven pharmacokinetic parameters [V_1, V_2, V_3, Cl_1, Cl_2, Cl_3, and lag time] × six hemodynamic factors [cardiac output, cardiac index, heart rate, stroke volume, mean arterial pressure, and systemic vascular resistance] = 42 scatter plots). Of these 42 combinations, only mean arterial pressure correlated significantly with V_1, V_2, Cl_1, Cl_3, and lag time. The results of these regressions are displayed in figure 4. The effect of mean arterial pressure was sequentially entered in the NONMEM model. The final results of this analysis are shown in table 2. The difference in $-2LL$ between the final model, including mean arterial pressure as covariate and the model without the covariates, was 61, which corresponds to $P < 0.0001$.
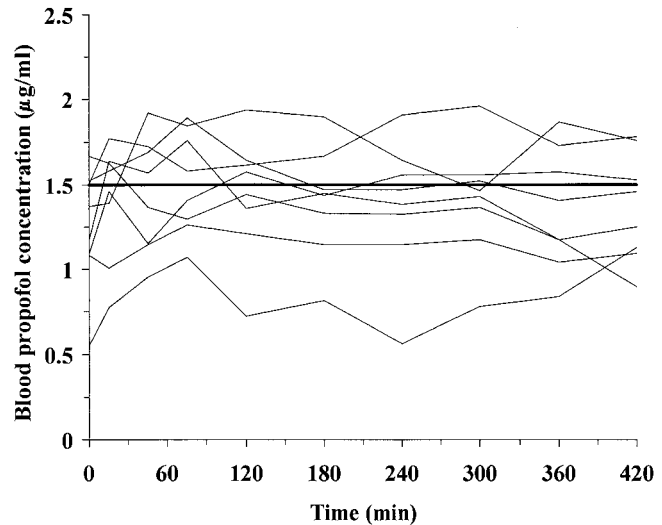
Fig. 2. Blood propofol concentration–time curves of all individual subjects during session B. The bold line represents the target propofol concentration of 1.5 μg/ml.

Hemodynamic Analysis

The mean hemodynamic parameters during sessions A and B are shown in table 3. The hemodynamic changes during and after administration of alfentanil in both sessions A and B are shown in figure 5. The addition of propofol resulted in a significantly lower mean arterial blood pressure ($P < 0.0001$), systemic vascular resistance ($P = 0.003$), and stroke volume ($P = 0.027$). The alfentanil infusion scheme caused all hemodynamic parameters except stroke volume to change significantly in time. In the presence of propofol this change in time was significantly altered for heart rate ($P < 0.0001$), stroke volume ($P = 0.007$), mean arterial pressure ($P = 0.004$), and systemic vascular resistance ($P = 0.007$).
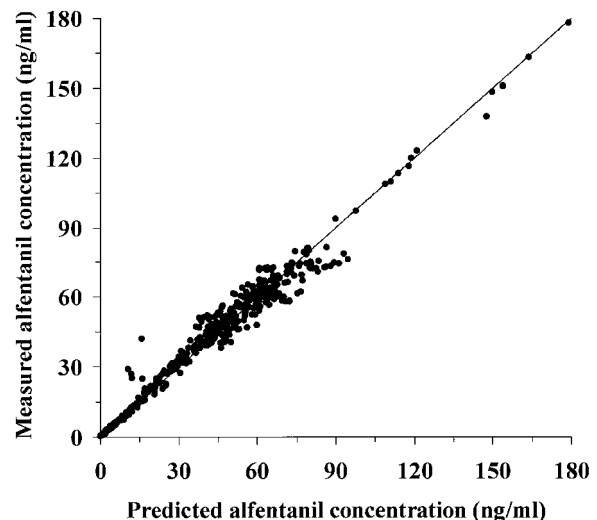

Fig. 3. Measured *versus* model-predicted plasma alfentanil concentrations, with propofol as covariate.

Table 1. Pharmacokinetic Parameters of Alfentanil (± SE) during Sessions A and B, Estimated by NONMEM with the Presence or Absence of Propofol as Covariate

Parameter	Session A (No Propofol)	Session B (with Propofol)	CV (%)
V_1 (ml/kg)	101 ± 18	101 ± 18	56
V_2 (ml/kg)	289 ± 33	289 ± 33	16
V_3 (ml/kg)	124 ± 16	124 ± 16	30
Cl_1 (ml · kg^{-1} · min^{-1})	6.1 ± 0.4	5.2 ± 0.4	25
Cl_2 (ml · kg^{-1} · min^{-1})	326 ± 139	104 ± 26	120
Cl_3 (ml · kg^{-1} · min^{-1})	3.0 ± 0.6	1.5 ± 1.1	20
t_{lag} (min)	1.88 ± 0.07	0.70 ± 0.08	91

The coefficient of variation was calculated as the square root of the variance of η.

CV = coefficient of variation; V_1 = central volume of distribution; V_2 = small peripheral volume of distribution; V_3 = large peripheral volume of distribution; Cl_1 = elimination clearance; Cl_2 = rapid distribution clearance; Cl_3 = slow distribution clearance; t_{lag} = lag time.

Computer Simulations

Computer simulations of the plasma alfentanil concentration after the alfentanil infusion scheme as used in this study (fig. 6) showed that the difference in plasma alfentanil concentration between sessions A and B ranged from 674 to 82% during the first 3 min after the start of the alfentanil infusion and increased from 3% at 3 min to 12% at the end of the alfentanil infusion. During the distribution and elimination phases, the difference in plasma alfentanil concentration between sessions A and B increased from 7% at 62 min to 88% at 420 min. The results of the simulation using the final pharmacokinetic model with propofol incorporated as covariate correspond very closely with the raw data (the measured plasma alfentanil concentration).

With alfentanil infusions longer than 6 min, the context-sensitive half-time of alfentanil is longer during combined infusion with propofol. Propofol increases the context-sensitive half-time of alfentanil by 3 min, on average, for durations of infusions ranging from 6 to 240 min (fig. 7).

Discussion

The aim of this study was to determine the influence of propofol on the pharmacokinetics of alfentanil. The blood propofol concentration was maintained constant both during and after the infusion of alfentanil, and this allowed us to evaluate the influence of propofol on both the distribution and elimination of alfentanil. As such, the study demonstrated that propofol decreased the lag time, the Cl_1, and both the Cl_2 and Cl_3 of alfentanil. Scaling lag time, V_1, V_2, Cl_1, and Cl_3 to mean arterial pressure resulted in a significantly better NONMEM model. The decrease in mean arterial blood pressure induced by propofol may have influenced the pharmacokinetics of alfentanil.

Critique on Methods

The study is based on venous sampling. Ethical considerations prohibited the introduction of arterial cannulae in volunteers and the infusion of drugs at concentrations that would cause subjects to lose consciousness. Therefore, only the influence of one level of propofol concentration was studied. Consequently, no conclusions can be drawn for propofol concentrations that lay outside the range encountered in this study.

Raw Data as Basis of the Pharmacokinetic Model

A lag time was incorporated in the three-compartment model in this study. A traditional pharmacokinetic compartmental model (without a lag time) significantly overestimated plasma alfentanil concentrations in the first blood samples, collected 2 and 3 min after the start of the alfentanil infusion. This overestimation may have been a result of the inability of the model to track correctly the alfentanil concentrations obtained from venous blood sampling. After administration of alfentanil in a forearm vein, it mixes within the venous blood, travels along the venous vasculature tree to the right heart, and is subject to first-pass effects in the lungs.[13–15] After distribution to the contralateral arm, the capillary bed of this arm is passed before reaching the point where the blood is sampled. To compensate for the time between the start of the alfentanil infusion and the first appearance of alfentanil in the venous blood sampled from the contralateral forearm, we introduced a lag time in the pharmacokinetic model. This lag time is similar to that used by Upton and Huang[16] to describe the indocyanine green concentration–time relationship in the pulmonary artery after administration in the inferior vena cava. In that study, lag time was inversely related to cardiac output, suggesting that a greater cardiac output was associated with a greater mean flow velocity between the injection site and the sampling site. In our study, the estimated lag time for alfentanil was considerably shorter in the presence of propofol. The significant reduction of systemic vascular resistance induced by propofol (fig. 5) may have led to a greater blood flow between the injection site and the sampling site.

In addition to a change in lag time, propofol also increased the initial peak plasma alfentanil concentration. In a sheep model, low cardiac output lead to higher peak concentrations after bolus injection because of slower drug–blood mixing.[16] In our study, however, cardiac output was similar in the presence and absence of propofol (fig. 5) and can therefore not explain the difference in the initial alfentanil concentration–time profile between sessions A and B. Alternatively, competition between alfentanil and propofol for tissue binding sites in the lungs and in the arm where alfentanil was sampled may have allowed a greater quantity of alfentanil to reach the veins of the contralateral arm during the first few minutes after administration of alfentanil in
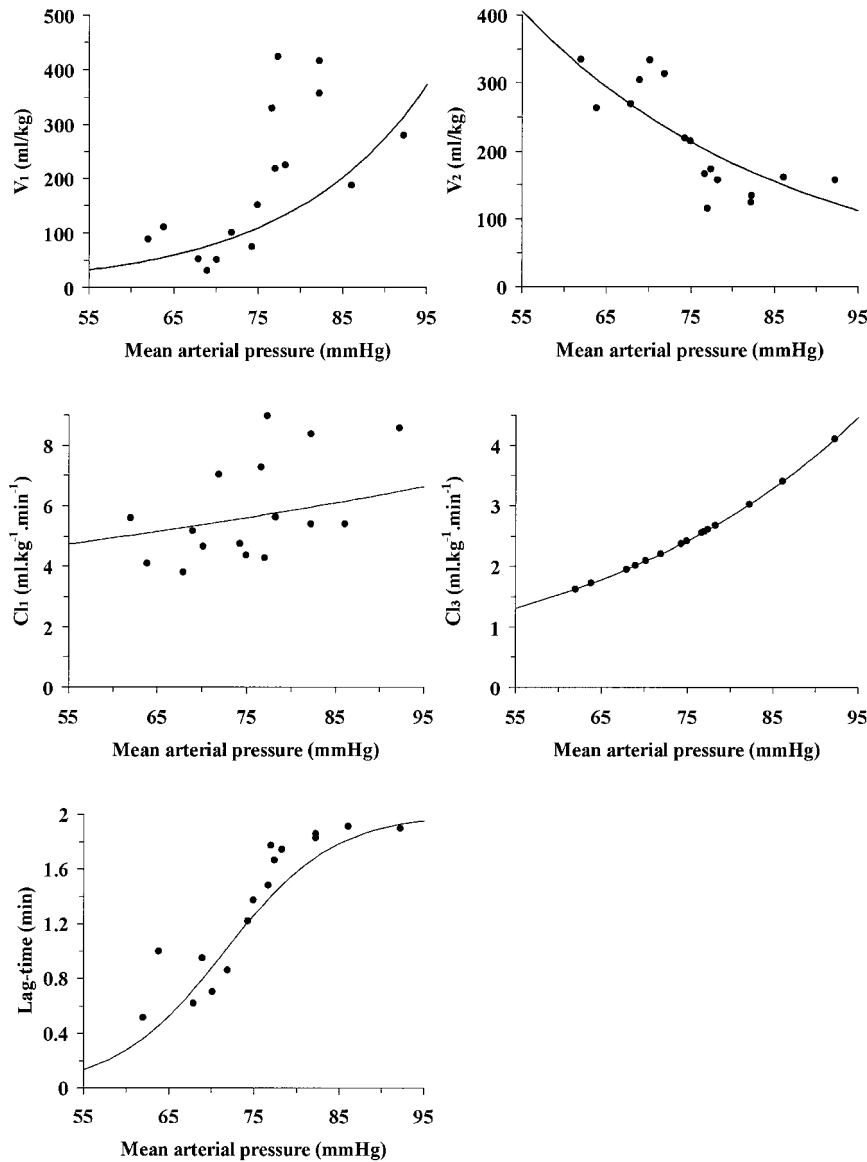
Fig. 4. The individual Bayesian estimates of central volume of distribution (V_1), small peripheral volume of distribution (V_2), elimination clearance (Cl_1), slow clearance (Cl_3), and lag time as a function of mean arterial pressure (dots). The relation between mean arterial pressure and V_1, V_2, Cl_1, Cl_3, and lag time (lines) was calculated using equations 2 and 4, with $\eta = 0$ (representing the typical individual) and α from table 2.

the presence of propofol than would have occurred when alfentanil was given alone. Both propofol and alfentanil have been shown to bind to lung tissue. Matot *et al.*[17] found that, in cats, 60% of an injected dose of propofol was extracted by the lung during a single passage through the pulmonary circulation. Propofol uptake was reduced to 40% by pretreatment with fentanyl. First-pass pulmonary uptake of alfentanil is reported to be between 10–20%[14,15] and 59%.[13] Like fentanyl, alfentanil may thus have competed with propofol in first-pass pulmonary uptake.

Interaction Mechanisms and Pharmacokinetic Model Parameters

When interpreting pharmacokinetic drug interactions, various mechanisms should be taken into consideration, including changes in plasma protein binding, tissue binding, hepatic enzyme activity, tissue–blood partitioning,

Table 2. The Population Pharmacokinetic Model of Alfentanil (± SE) with Mean Arterial Pressure as Covariate

Parameter	Typical Value	α	CV (%)
V_1 (ml/kg)	115 ± 7.64	0.0612 ± 0.00584	86
V_2 (ml/kg)	208 ± 40.4	−0.0321 ± 0.0199	25
V_3 (ml/kg)	136 ± 23.2	0	27
Cl_1 (ml · kg^{-1} · min^{-1})	5.64 ± 0.385	0.00839 ± 0.00594	23
Cl_2 (ml · kg^{-1} · min^{-1})	73.8 ± 5.75	0	—
Cl_3 (ml · kg^{-1} · min^{-1})	2.48 ± 0.671	0.0306 ± 0.0191	—
t_{lag} (min)	1.32 ± 0.0676	0.158 ± 0.0146	45

The coefficient of variation was calculated as the square root of the variance of η. With $\alpha = 0$, mean arterial pressure is not a significant covariate.

CV = coefficient of variation; V_1 = central volume of distribution; V_2 = small peripheral volume of distribution; V_3 = large peripheral volume of distribution; Cl_1 = elimination clearance; Cl_2 = rapid distribution clearance; Cl_3 = slow distribution clearance; t_{lag} = lag time.

Table 3. Mean Hemodynamic Parameters Obtained during the 420-min Study Period in Sessions A and B (with Propofol), Compared with the Paired Sample *t* Test

Parameter	Session A	Session B	Mean Difference	Significance (*P* Value)
CO (l/min)	6.4 ± 0.7	6.1 ± 0.8	−0.3 ± 0.7	0.248
CI ($l \cdot min^{-1} \cdot m^{-2}$)	3.3 ± 0.4	3.1 ± 0.4	0.2 ± 0.4	0.284
HR (beats/min)	57 ± 10	56 ± 7	−1 ± 9	0.802
SV (ml/beat)	114 ± 14	109 ± 16	−5 ± 10	0.231
MAP (mmHg)	81 ± 6	69 ± 5	−12 ± 4	0.000
SVR ($dyne \cdot s \cdot cm^{-5}$)	1,008 ± 107	908 ± 109	−100 ± 121	0.053

CO = cardiac output; CI = cardiac index; HR = heart rate; SV = stroke volume; MAP = mean arterial pressure; SVR = systemic vascular resistance.

and tissue perfusion. Of these, plasma protein binding is probably of little importance. Because propofol and alfentanil bind to different plasma proteins (albumin and α_1-acid glycoprotein, respectively), interactions at this level are not likely.

In this study, propofol was found to decrease the Cl_1, Cl_2, and Cl_3 of alfentanil. The primary site of alfentanil metabolism is the liver, where it is metabolized by cytochrome P450 3A3/4,[18,19] while less than 0.5% appears in the urine unchanged.[20] Reported hepatic extraction ratios for alfentanil vary from 0.3 to 0.5.[2,21,22] Because of this intermediate hepatic extraction ratio, changes in hepatic blood flow may
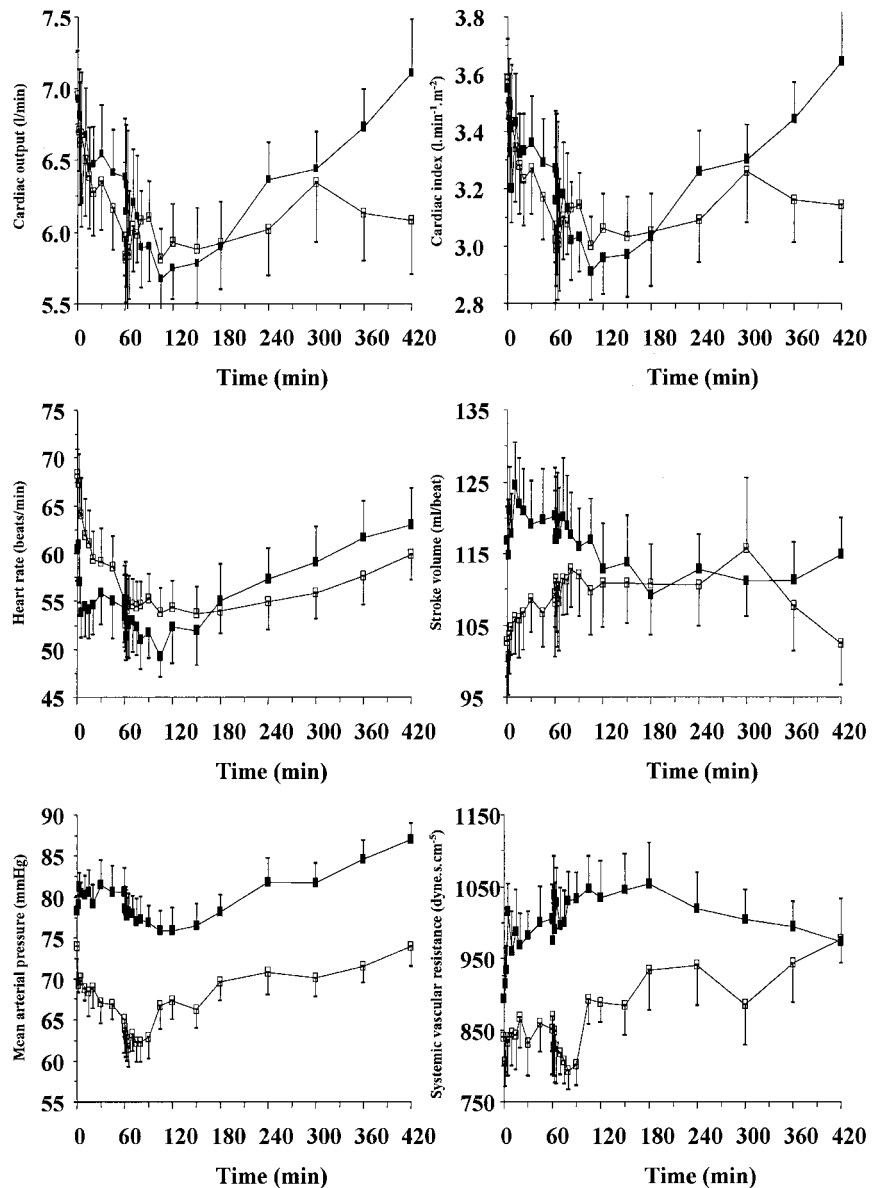

Fig. 5. The mean (± SE) hemodynamic parameters *versus* time data in the presence (open squares) and absence (closed squares) of propofol.
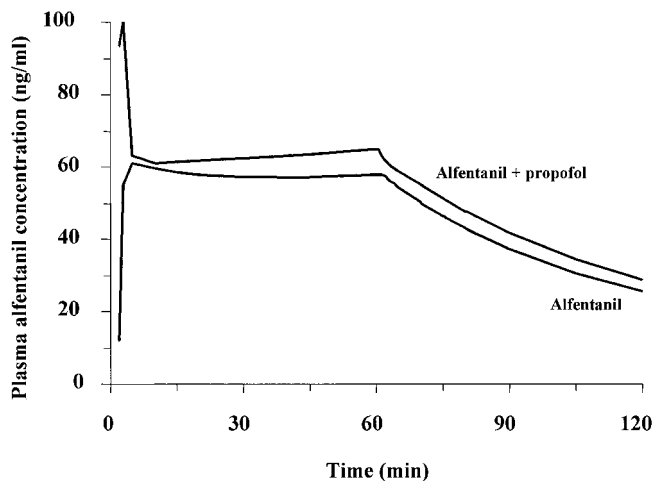
Fig. 6. Computer simulation of the plasma alfentanil concentration with the infusion scheme used in this study (12.5 µg/kg intravenous alfentanil, administered in 2 min, followed by 25 µg · kg^{-1} · h^{-1} for 58 min).
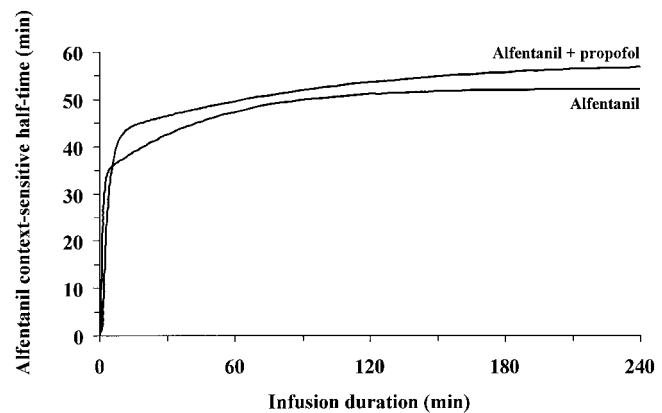

Fig. 7. The context-sensitive half-times of alfentanil *versus* infusion duration in the presence and absence of a propofol target controlled infusion with a target concentration of 1.5 µg/ml, using the pharmacokinetic model with propofol incorporated as covariate, for infusion durations up to 240 min.

have some effect on the clearance of alfentanil. In a physiologic model, Björkman *et al.*[23] simulated the effect of hepato-splanchnic blood flow fluctuations of ± 50% of the baseline value on arterial plasma alfentanil concentrations during alfentanil infusion. In the presence of these blood flow fluctuations, alfentanil concentrations varied ± 12%. The reduction in systemic vascular resistance by the addition of propofol, as observed in our study, is most likely the result of arterial and venous vasodilatation caused by inhibition of tonic sympathetic vasoconstrictor outflow.[24-28] This may have led to an increase in the perfusion of peripheral tissues at the expense of the perfusion of central tissues. The resultant reduction of hepato-splanchnic blood flow may, at least in part, explain the reduced clearance of alfentanil in the presence of propofol. However, the literature regarding the effect of propofol on hepato-splanchnic blood flow is not conclusive.[29-31] In addition, modulation of cytochrome P450 activity may have resulted in alterations of the metabolism as well and consequently may have reduced the clearance of alfentanil. Indeed, propofol is known to inhibit the activity of cytochrome P450 3A[32] and has been shown to be a potent inhibitor of human liver microsomal metabolism of alfentanil.[33] In the absence of propofol, the value of Cl_2 of alfentanil estimated by NONMEM is so large that the model behaves more or less as if it were a two-compartment model. It is our impression that NONMEM had difficulty describing the early phase of the plasma alfentanil–time profile with a three-compartment model and tried to improve the fit by increasing Cl_2. A three-compartment model may not be the best choice to describe the early phase of distribution.

Propofol caused a significant reduction in the mean arterial pressure and systemic vascular resistance. Although systemic vascular resistance is probably the parameter that is actually influencing the pharmacokinetics of alfentanil, it was only mean arterial pressure that

correlated significantly with any of the Bayesian estimates of the interindividual variability term (η). Therefore, mean arterial pressure was entered in the NONMEM model as covariate. Scaling the pharmacokinetic parameters to the mean arterial pressure resulted in a better model according to the $-2LL$ criterion than scaling the pharmacokinetic parameters to the presence or absence of propofol. We therefore conclude that it is very likely that changes in the mean arterial pressure, and therefore the systemic vascular resistance, induced by propofol may have an important influence on the pharmacokinetics of alfentanil.

Computer simulations of the plasma alfentanil concentration after the alfentanil infusion scheme as used in this study showed that the difference in plasma alfentanil concentration between sessions A and B ranged from 674 to 82% during the first 3 min after the start of the alfentanil infusion and increased from 3% at 3 min to 12% at the end of the alfentanil infusion. During the distribution and elimination phases, the difference in plasma alfentanil concentration between sessions A and B increased from 7% at 62 min to 88% at 420 min.

The implication of this study is that when alfentanil is administered in combination with propofol (*e.g.*, during induction), the plasma alfentanil concentration will initially be considerably higher than would be expected from pharmacokinetic parameters of alfentanil that are determined in the absence of propofol. After this initial peak difference, the difference between the expected and observed plasma alfentanil concentration will be relatively small in comparison with the pharmacodynamic variability. This difference will therefore not be very clinically relevant.

Caution is required when extrapolating the results of the present study to combinations of propofol and other opioids, such as fentanyl or sufentanil. Fentanyl and sufentanil are characterized by higher extraction ratios

compared with alfentanil. Therefore, the clearance of these agents is more likely to be influenced by changes in hepatic perfusion. Consequently, the hemodynamic changes induced by propofol may reduce the clearance of sufentanil and fentanyl to a greater degree and thereby increase their concentrations to a greater extend compared with alfentanil.

In conclusion, this study demonstrates that propofol alters the pharmacokinetics of alfentanil. The changes in cardiovascular function induced by propofol may have an important influence on the pharmacokinetics of alfentanil.

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Appendix: Assigning a Probability Distribution to the Lag Time

Interindividual variability terms (ηs) are assumed in NONMEM to be normally distributed. For the lag time it was necessary to construct a distribution on the domain (0,2). This was accomplished by mapping this domain to ($-\infty,\infty$) using the logit function:

$$f(x) = \ln\left(\frac{\frac{x}{2}}{1 - \frac{x}{2}}\right) \quad (3)$$

The model for lag time reads:

$$t_{lag} = f'(f(t_{lag,typical}) + \eta_{T_{lag}} + \alpha \cdot (\text{covariate} - \text{median of covariate})) \quad (4)$$

where f' is the inverse of f.