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# *Mixed-effects Modeling of the Influence of Alfentanil on Propofol Pharmacokinetics*

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

***Methods:*** **The pharmacokinetics of propofol were studied on two occasions in eight male volunteers in a randomized crossover manner with a 3-week interval. While volunteers breathed 30% $O_2$ in air, 1 mg/kg intravenous propofol was given in 1 min, followed by 3 mg · kg$^{-1}$ · h$^{-1}$ for 59 min (sessions A and B). During session B, a target-controlled infusion of alfentanil (target concentration, 80 ng/ml) was given from 10 min before the start until 6 h after termination of the propofol infusion. Blood pressure, cardiac output, electrocardiogram, respiratory rate, oxygen saturation, and end-tidal carbon dioxide were monitored. Venous blood samples for determination of the blood propofol and plasma alfentanil concentration were collected until 6 h after termination of the propofol infusion. Nonlinear mixed-effects population pharmacokinetic models examining the influence of alfentanil and hemodynamic parameters on propofol pharmacokinetics were constructed.**

***Results:*** **A two-compartment model, including a lag time accounting for the venous blood sampling, adequately described the concentration–time curves of propofol. Alfentanil decreased the elimination clearance of propofol from 2.1 l/min to 1.9 l/min, the distribution clearance from 2.7 l/min to 2.0 l/min, and the peripheral volume of distribution from 179 l to 141 l. Scaling the pharmacokinetic parameters to cardiac output, heart rate, and plasma alfentanil concentration significantly improved the model.**

***Conclusions:*** **Alfentanil alters the pharmacokinetics of propofol. Cardiac output and heart rate have an important influence on the pharmacokinetics of propofol.**

IN anesthetic practice, propofol is frequently combined with alfentanil 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.[1–6] More recently, pharmacodynamic interactions between propofol and alfentanil have been reported.[7,8] These studies showed 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. Pavlin *et al.*[9] reported that plasma propofol concentrations were higher in the presence of alfentanil than in the absence of alfentanil. Enhanced propofol concentrations have also been reported in the presence of fentanyl[10] and sufentanil.[11] The mechanisms of the interaction, the precise magnitudes, and the clinical relevance have not been resolved. We therefore studied the pharmacokinetics of propofol, given in the presence and absence of a pseudo–steady state plasma alfentanil concentration, in eight healthy male volunteers. In addition, changes in the hemodynamics during and after the propofol infusion were studied in the presence and absence of alfentanil, and the influence of hemodynamic variables on the pharmacokinetics of propofol were examined.

## Materials and Methods

### *Volunteers and Study Protocol*

After obtaining approval from the Medical Ethics Committee of the Leiden University Medical Center (Leiden, The Netherlands) and informed consent, eight healthy male volunteers, aged 20–30 yr, participated in the study. The volunteers were within 30% of 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 alcohol or smoking more than 10 cigarettes/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 1 mg/kg intravenous propofol in 1 min, followed by an infusion of 3 mg · kg$^{-1}$ · h$^{-1}$ for 59 min (control, session A). On the other occasion, they received the same dosing regimen of propofol in the presence of a target-controlled alfentanil infusion with a target alfentanil concentration of 80 ng/ml. This was started 10 min before the start and maintained until 6 h after the termination of the propofol 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. The study sessions were separated by a 3-week interval.

Volunteers fasted from midnight before the study until the last blood sample had been collected. During the administration of propofol, they breathed 30% oxygen in

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air. When indicated, ventilation was assisted using a facemask to maintain the end-tidal partial pressure below 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.

Propofol was administered with a conventional infusion pump. Prestudy computer simulations showed that the effect site propofol concentration was not likely to exceed 1.5 $\mu$g/ml, allowing spontaneous ventilation. A pocket computer, provided with three-compartment pharmacokinetic parameters of alfentanil[1] was used to control[12] an infusion pump for the target-controlled infusion of alfentanil.

Blood pressure was measured noninvasively, and the electrocardiogram, respiratory rate, peripheral oxygen saturation, and end-tidal carbon dioxide partial pressure were monitored continuously throughout the study. Cardiac output was measured noninvasively using a thoracic bioimpedance system (IQ system; Renaissance Technology, Newton, PA). The systemic vascular resistance was calculated from the mean arterial pressure and cardiac output. All adverse events were recorded.

*Blood Samples and Assays*

Blank venous blood samples for calibration purposes (8 ml) were obtained before the start of the propofol infusion. Additional blood samples (3 ml) for the determination of the blood propofol concentrations were collected 1, 3, 5, 10, 20, 30, 45, and 60 min after the start of the propofol 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 propofol 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.[13] The coefficient of variation of this method was 3% or less in the concentration range encountered in this study. The limit of detection was 11.7 ng/ml. Propofol assays were conducted within 12 weeks.

During session B, additional blood samples (5 ml) for determination of plasma alfentanil concentrations were collected before the start of the alfentanil infusion; 15, 45, 75, and 120 min after the start of the propofol infusion; and then at hourly intervals until 6 h after termination of the propofol 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.[14] The coefficient of variation of this method was 4% or less in the concentration range encountered in this study. The limit of detection was 0.8 ng/ml.

*Analysis of Hemodynamic Data*

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

*Pharmacokinetic and Statistical Analysis*

Data analysis was performed using an approach combining Bayesian regression and NONMEM population analysis similar to that previously described by Maitre *et al.*[15] Population pharmacokinetic parameters were estimated with the computer program NONMEM (version V, level 1.1; The NONMEM Project Group, University of California, San Francisco, CA), using the first-order conditional estimation method with $\eta - \epsilon$ interaction for two- (ADVAN3) and three-compartment (ADVAN11) models with and without lag time.[16] A proportional error model was used with variance $\sigma^2$ of the intraindividual variability terms ($\epsilon$). The interindividual variability of each of the model parameters (central volume of distribution [$V_1$], shallow peripheral volume of distribution [$V_2$], deep peripheral volume of distribution [$V_3$], elimination clearance [$Cl_1$], rapid distribution clearance [$Cl_2$], slow distribution clearance [$Cl_3$], and lag time [$t_{lag}$]) was specified using a log normal variance model:

$$\Theta_i(t) = \Theta_{TV} \cdot e^{(\eta_i + \sum_{j=1}^{m} \alpha_j (\mathrm{cov}_{ji}(t) - MD\mathrm{cov}_j))} \quad (1)$$

where $\Theta_i(t)$ is the value of the pharmacokinetic parameter in individual $i$ at time $t$, $\Theta_{TV}$ is the typical value of the pharmacokinetic parameter in the population, $\eta i$ is the Bayesian estimate for the normally distributed random variable $\eta$ (with mean zero and variance $\omega^2$) in individual $i$ (which is estimated by NONMEM), $m$ is the number of covariates considered, $\alpha_j$ is the value of the parameter (coefficient) describing the dependence of the pharmacokinetic parameter on covariate $j$, $\mathrm{cov}_{ji}(t)$ is the value of covariate $j$ in individual $i$ at time $t$, and $MD\mathrm{cov}_j$ is the median of covariate $j$ in the population. $MD\mathrm{cov}_j$ is the median of 16 observations (8 volunteers × 2 sessions), except for the alfentanil concentration, for which it represents the median of 8 observations (8 volunteers during session B only). Potential covariates examined in this study were the mean plasma alfentanil concentration over the entire study period (a time-independent covariate) and hemodynamic parameters (all time-dependent covariates; see below). Coefficients of

variation were calculated as the square root of the variance $\omega^2$ of $\eta$ and, parameter distributions being asymmetric, are only approximately the coefficients of variation as usually defined.

First, two- and three-compartment models with and without a lag time to compensate for the venous sampling, but without covariates (*i.e.*, with all $\alpha_j = 0$) were examined. The models were examined and compared based on the Akaike information-theoretic criterion (AIC $= -2 \times$ log likelihood [LL] + 2p, where p is the number of parameters in the model)[17] and by inspection of the SEs of the parameters. All subsequent analyses were based on a two-compartment model with a lag time.

*Inclusion Procedure for Covariates*

Potential covariates examined were the plasma alfentanil concentration, cardiac output, stroke volume, heart rate, mean arterial blood pressure, and systemic vascular resistance. First, the mean values of the potential covariates over the entire study period were calculated for each volunteer and session. Subsequently, the relation between the Bayesian estimates of the pharmacokinetic parameters of the two-compartment model with lag time, but without covariates, and the mean values of potential covariates were examined by linear regression analysis. From then on, only those potential covariates that showed a significant ($P < 0.05$) correlation with at least one pharmacokinetic parameter (*i.e.*, the plasma alfentanil concentration, cardiac output, and heart rate; see also Results section) were included in further analyses. In the further analyses, the plasma alfentanil concentration (mean value in each volunteer over the entire study period) was treated as a time-independent covariate, whereas cardiac output and heart rate were treated as time-dependent covariates. For these covariates, the arithmetic mean values during consecutive intervals between blood sampling times were calculated and, along with the blood concentrations in the samples collected at the end of the intervals, were used as the input for the NONMEM analysis.

The first analyses involving covariates examined individual covariates, whereby all possible 32 combinations (with the covariate associated with any combination of one, two, three, four, or all five pharmacokinetic parameters) were explored and the combination that resulted in the lowest value of AIC was considered optimal and selected for further explorations. Then, the plasma alfentanil concentration was added as a potential second covariate to the selected models based on either cardiac output or heart rate as a primary covariate. In addition, heart rate was added as a potential second covariate to the selected model based on cardiac output as a primary covariate. Finally, the model including cardiac output and heart rate as covariates was further extended, with the plasma alfentanil concentration as a potential third covariate. In the secondary and tertiary analyses, the newly added covariate was examined by again exploring all possible 32 combinations, with the covariate(s) already in the model being associated only with those parameters to which it was already associated in the model without the newly added covariate. Models with covariates were compared on the basis of the AIC.

To estimate the accuracy of the model, we calculated the weighted residual (WR) and the absolute weighted residual (AWR) for each sample:

$$WR_{ij} = \frac{C_{meas,ij} - C_{pred,ij}}{C_{pred,ij}} \quad AWR_{ij} = \frac{|C_{meas,ij} - C_{pred,ij}|}{C_{pred,ij}} \tag{2}$$

in which $C_{meas,ij}$ is the *j*th measured concentration of the *i*th individual, and $C_{pred,ij}$ denotes the corresponding predicted value. The median population values of the WR (median weighted residual [MDWR]) and of the AWR (median absolute weighted residual [MDAWR]) were used as overall measures of goodness of fit.

*Computer Simulations*

The implications of the pharmacokinetic interaction between propofol and alfentanil were explored by computer simulations using the determined pharmacokinetic parameters of propofol for a 70-kg man. Blood propofol concentrations, in the absence and presence of the median measured plasma alfentanil in session B, were simulated according to the propofol infusion scheme used in this study. The context-sensitive half-times (*i.e.*, the time needed for a blood concentration to decrease by 50% after termination of a target controlled infusion) of propofol in the absence and presence of the median measured plasma alfentanil in session B were calculated for target-controlled infusions with a constant target concentration lasting 0–90 min.

*Statistical Analysis*

Mean values of hemodynamic parameters over the entire study period during session A and session B were compared using the paired *t* test. $P < 0.05$ was considered significant.

## Results

All eight volunteers completed the study without adverse events. In two subjects, the propofol infusion was terminated after 40 min during the first session (session B in both subjects) because the level of sedation and respiratory depression were more profound than anticipated and approved by the Medical Ethics Committee. In these two volunteers, the second (control) session was also limited to a 40-min propofol infusion.

The mean (± SD) age, weight, and height of the volunteers were 24 ± 3 yr, 70 ± 4 kg, and 1.87 ± 0.03 m, respectively. Plasma alfentanil concentrations were sta-

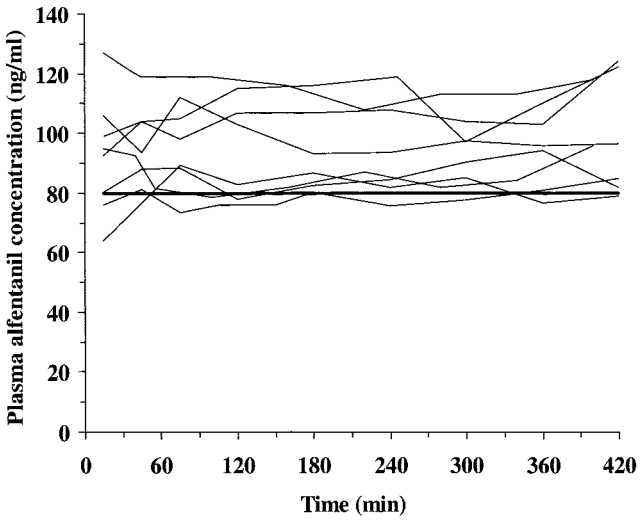


**Fig. 1. Plasma alfentanil concentration–time curves of all individual subjects during session B. The *thick line* represents the target alfentanil concentration of 80 ng/ml.**

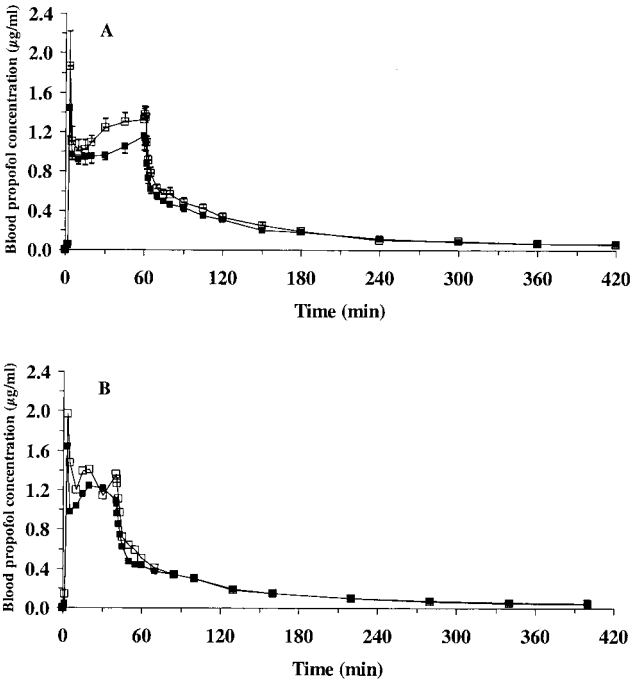


**Fig. 2. Mean (± SE) blood propofol concentration-*versus*-time data in the presence (*open squares*) and absence (*closed squares*) of alfentanil in the subjects with a 60-min propofol infusion scheme (*A*). Mean blood propofol concentration-*versus*-time data in the presence (*open squares*) and absence (*closed squares*) of alfentanil in the two subjects with a 40-min propofol infusion scheme (*B*).**

ble over time (fig. 1). Mean plasma alfentanil concentrations calculated from all collected blood samples per subject ranged from 78.2 to 117.1 ng/ml in the eight volunteers. Table 1 shows the mean hemodynamic parameters obtained over the 420-min study period in sessions A (without alfentanil) and B (with alfentanil). The only hemodynamic parameter that differed significantly between sessions A and B was heart rate ($P$ = 0.02).

A total of 428 blood samples for blood propofol concentration analysis were collected and used in the pharmacokinetic analysis. Figure 2 shows the measured blood propofol concentrations during the study period in the presence and absence of alfentanil. During propofol infusion, measured blood propofol concentrations were 18% higher in the presence than in the absence of alfentanil. From the time of the termination of the propofol infusion until 6 h thereafter, the measured blood propofol concentrations were on average 16% higher in the presence than in the absence of alfentanil.

*Pharmacokinetic Analysis*

Although a three-compartment model resulted in a better fit according to the AIC, the SEs of some estimated parameters were unacceptably large. Therefore, the two-compartment model with a lag time was selected to describe the concentration–time profile of propofol in both sessions. The results of the two-compartment analysis are presented in table 2, which provides in columns 1 and 2 the estimates of the population pharmacokinetic parameters for propofol without covariates and with the plasma alfentanil concentration incorporated into the model as a covariate. The NONMEM analysis determined the plasma alfentanil concentration as a significant covariate on $Cl_1$, $Cl_2$, and $V_2$. The AIC of this model was lower than that of the model without covariates (4,141.8 and 4,150.0, respectively). The MDWR and MDAWR for the model without covariates were −1.4 and 17.9%, respectively, and were −0.9 and 16.4% for the model with the plasma alfentanil concentration as a covariate.

**Table 1. Mean Hemodynamic Parameters Obtained during the 420-min Study Period in Sessions A (without Alfentanil) and B (with Alfentanil)**

| Parameter | Session A | Session B | Mean Difference | *P* Value |
|---|---|---|---|---|
| CO, l/min | 7.0 ± 1.6 | 6.7 ± 0.9 | 0.3 ± 1.0 | 0.34 |
| HR, beats/min | 63 ± 7 | 58 ± 7 | 5 ± 5 | 0.02 |
| SV, ml/beat | 112 ± 16 | 117 ± 13 | −5 ± 8 | 0.15 |
| MAP, mmHg | 86 ± 6 | 81 ± 7 | 5 ± 8 | 0.10 |
| SVR, dyn · s · $cm^{-5}$ | 987 ± 156 | 967 ± 135 | 20 ± 137 | 0.69 |

Data were compared with the paired sample *t* test. Data are presented as mean ± SD.

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

Individual Bayesian pharmacokinetic parameters were obtained from the model without covariates and plotted against the individual mean plasma alfentanil concentration as well as the mean hemodynamic parameters over the duration of each session. Of these 30 combinations (5 pharmacokinetic parameters [$Cl_1$, $Cl_2$, $V_1$, $V_2$, and lag time] $\times$ 6 potential covariates [plasma alfentanil concentration, cardiac output, heart rate, stroke volume, mean arterial pressure, and systemic vascular resistance] = 30 scatter plots), plasma alfentanil concentration correlated significantly with $Cl_1$; cardiac output correlated significantly with $Cl_1$, $V_2$, and lag time; and heart rate correlated significantly with $Cl_1$ and $V_2$ ($P < 0.05$). The results of the regressions including plasma alfentanil concentration, cardiac output, and heart rate are displayed in figure 3. Because lag time increased only 0.05 min over the cardiac output range encountered in this study, its influence on lag time was judged as clinically insignificant. Therefore, this scatter plot is not shown.

The best models, which included cardiac output, heart rate, or both as covariates instead of or in addition to plasma alfentanil concentration, are presented in table 2. The median cardiac output, heart rate, and plasma alfentanil concentration used in the pharmacokinetic modeling were 6.3 l/min, 58 beats/min, and 92.7 ng/ml, respectively (equation 1). The AIC of the final extended model, which incorporated cardiac output, heart rate, and plasma alfentanil concentration as covariates, was lower than that of the model with plasma alfentanil concentration as the only covariate (4,114.9 and 4,141.8, respectively). Values of the MDWR and MDAWR in individual subjects during each session are presented in figure 4. It shows that with each reduction in the AIC of the model, the range of the individual MDWR and MDAWR values decreases. Figure 5 shows the weighted residuals plotted *versus* time, calculated for the model with plasma alfentanil, cardiac output, and heart rate incorporated as covariates (table 2). The population MDWR and MDAWR for the final model were −0.5 and 16.4%, respectively, compared with −0.9 and 16.4% for the model with the plasma alfentanil concentration as the only covariate.

*Computer Simulations*

Computer simulations of the propofol infusion scheme used in this study, based on the pharmacokinetic model with the plasma alfentanil concentration as the only covariate, showed that the difference in blood propofol concentration between sessions A and B during the propofol infusion increased from 5% at 3 min to 18% at the end of the infusion (fig. 6). After stopping the infusion, the difference in blood propofol concentration between sessions A and B ranged from 10% to 25% after 6 h.

The context-sensitive half-time of propofol is longer during combined infusion with alfentanil. Alfentanil increases the context-sensitive half-time of propofol by up to 2 min for durations of infusion up to 90 min (fig. 7).

## Discussion

The primary objective of this study was to determine the influence of alfentanil on the pharmacokinetics of propofol. The study showed that alfentanil decreased $Cl_1$, $Cl_2$, and $V_2$ of propofol. In addition, the influence of hemodynamic parameters was investigated. This showed that both cardiac output and heart rate affect the pharmacokinetics of propofol. The final model included cardiac output as a time-dependent covariate affecting $Cl_1$, $Cl_2$, $V_1$, and $V_2$ and heart rate as a time-dependent covariate affecting $Cl_1$, $Cl_2$, and $V_2$. However, changes in cardiac output and heart rate could not completely explain the effects of alfentanil because the final model also included the plasma alfentanil concentration as a covariate.

*Critique on Methods*

The study is based on venous sampling. Ethical considerations prohibited the introduction of arterial cannulae in volunteers and the administration of drugs to an extent that subjects would lose consciousness. Plasma concentrations in the sample collected 1 min after starting the infusion were mostly very low (< 86.0 ng/ml) and poorly fitted by both two- and three-compartment models without inclusion of a lag time. Therefore, a lag time[16] was incorporated in the two-compartment model to compensate for the time between the start of the propofol infusion and the first appearance of propofol in the venous blood sampled from the contralateral forearm. Plasma alfentanil concentration was not identified as a significant covariate on lag time, nor was cardiac output or heart rate. The impact of venous blood sampling on propofol pharmacokinetics has been investigated by Schüttler *et al.*[2] In their final three-compartment population pharmacokinetic model, based on 4,112 arterial and venous blood samples, venous blood sampling was included as a significant covariate on the rapid distribution clearance ($Cl_2$), which was smaller for venous sampling.

In this study, the influence of alfentanil concentration was studied only in the range from 78.2 to 117.1 ng/ml. Consequently, no conclusions can be drawn for alfentanil concentrations outside the range encountered in this study.

The median measured plasma alfentanil concentration in session B was 92.7 ng/ml, somewhat higher than the set target alfentanil concentration of 80 ng/ml. This may be explained by the influence of propofol on the pharmacokinetics of alfentanil, as described recently.[16]

*Pharmacokinetic Modeling*

The pharmacokinetic model of propofol without covariates was improved by scaling the pharmacokinetic

**Table 2. Population Pharmacokinetic Models of Propofol**

| | No Covariates | | Alfentanil | | CO | | HR | |
|---|---|---|---|---|---|---|---|---|
| Parameter | Value | %CV | Value | %CV | Value | %CV | Value | %CV |
| $V_1$, l | 43.6 ± 5.6 | 43 | 43.4 ± 5.4 | 42 | 38.7 ± 5.1 | 44 | 38.5 ± 5.4 | 44 |
| $V_2$, l | 158.2 ± 9.7 | 21 | 140.7 ± 11.3 | 18 | 157.5 ± 6.9 | 16 | 165.2 ± 7.3 | 15 |
| $Cl_1$, l/min | 2.0 ± 0.1 | 11 | 1.9 ± 0.1 | 9 | 1.9 ± 0.1 | 9 | 2.0 ± 0.0 | 7 |
| $Cl_2$, l/min | 2.3 ± 0.2 | 31 | 2.0 ± 0.2 | 27 | 2.4 ± 0.2 | 29 | 2.4 ± 0.2 | 30 |
| $t_{lag}$, min | 0.96 ± 0.01 | 3 | 0.96 ± 0.01 | 2 | 0.96 ± 0.01 | 3 | 0.96 ± 0.01 | 3 |
| Covariates | | | | | | | | |
| $\alpha_{ALFC,V_1}$ | | | | | | | | |
| $\alpha_{ALFC,V_2}$ | | | −0.0026 | | | | | |
| $\alpha_{ALFC,Cl_1}$ | | | −0.0014 | | | | | |
| $\alpha_{ALFC,Cl_2}$ | | | −0.0033 | | | | | |
| $\alpha_{ALFC,lag\ time}$ | | | | | | | | |
| $\alpha_{CO,V_1}$ | | | | | 0.0952 | | | |
| $\alpha_{CO,V_2}$ | | | | | 0.1240 | | | |
| $\alpha_{CO,Cl_1}$ | | | | | 0.0414 | | | |
| $\alpha_{CO,Cl_2}$ | | | | | 0.1010 | | | |
| $\alpha_{CO,lag\ time}$ | | | | | | | | |
| $\alpha_{HR,V_1}$ | | | | | | | 0.0113 | |
| $\alpha_{HR,V_2}$ | | | | | | | 0.0198 | |
| $\alpha_{HR,Cl_1}$ | | | | | | | 0.0109 | |
| $\alpha_{HR,Cl_2}$ | | | | | | | 0.0175 | |
| $\alpha_{HR,lag\ time}$ | | | | | | | | |
| Performance measures | | | | | | | | |
| −2 LL | 4,140.0 | | 4,125.8 | | 4,113.1 | | 4,100.4 | |
| AIC | 4,162.0 | | 4,153.8 | | 4,143.1 | | 4,130.4 | |
| MDWR, % | −1.4 | | −0.9 | | −0.2 | | −0.8 | |
| MDAWR, % | 17.9 | | 16.4 | | 16.7 | | 17.6 | |

$\alpha$ = measure of covariate importance (when $\alpha$ is omitted, the covariate is not significant); AIC = Akaike information-theoretic criterion[17]; ALFC = concentration of alfentanil; $Cl_1$ = elimination clearance; $Cl_2$ = distribution clearance; CO = cardiac output; CV = coefficient of variation; HR = heart rate; −2 LL = −2 × log likelihood; MDAWR = median absolute weighted residual; MDWR = median weighted residual; $t_{lag}$ = lag time; $V_1$ = central volume of distribution; $V_2$ = peripheral volume of distribution.

parameters $Cl_1$, $Cl_2$, and $V_2$ to the plasma alfentanil concentration.

In the extended model, plasma alfentanil concentration as well as cardiac output and heart rate could be incorporated because they affected the individual Bayesian pharmacokinetic parameters. Eventually, cardiac output was incorporated in the final extended model as a time-dependent covariate affecting $Cl_1$, $Cl_2$, $V_1$, and $V_2$; heart rate was incorporated as a time-dependent covariate affecting $Cl_1$, $Cl_2$, and $V_2$; and plasma alfentanil concentration was incorporated as a covariate on $Cl_1$ and $V_2$.

In this study, changes in cardiac output and heart rate were induced by the infusion of propofol during both sessions A and B and by the administration of alfentanil during session B. Furthermore, alfentanil may have altered the hemodynamic changes induced by propofol. Consequently, the effects of cardiac output and heart rate on the pharmacokinetic parameters of propofol may well be present, even in the absence of alfentanil.

The initial volume of distribution in this study is somewhat larger than in most other studies on the pharmacokinetics of propofol, whereas the steady state volume of distribution is somewhat smaller. Clearance values are grossly comparable. The differences in $V_1$ are most likely explained by the differences in modeling (two *vs.* three compartments) and by the differences in the duration of blood sampling.

### *Interaction Mechanisms and Pharmacokinetic Model Parameters*

Changes in plasma protein binding, tissue binding, hepatic enzyme activity, tissue–blood partitioning, and tissue perfusion may explain pharmacokinetic drug interactions. Of these, plasma protein binding is probably of little importance. Because propofol and alfentanil bind to different plasma proteins (albumin[18,19] and $\alpha_1$-acid glycoprotein,[14] respectively), interactions at this level are unlikely.

The final model predicts that the peripheral volume of distribution ($V_2$) and the distribution clearance ($Cl_2$) increase with increasing cardiac output and heart rate. The final model also predicts that $V_2$ decreases with an increasing plasma alfentanil concentration. Because the primary determinant of the distribution and redistribution is tissue blood flow, the rate at which a drug is transported to and from any tissue or part of the body is directly proportional to the cardiac output. This has been confirmed for thiopental and alfentanil. Henthorn *et al.* suggested that the distribution of thiopental[20] was dependent on cardiac output and described the relation between cardiac output and the tissue distribution of

**Table 2. (continued)**

| CO + Alfentanil | | HR + Alfentanil | | CO + HR | | CO + HR + Alfentanil | |
|---|---|---|---|---|---|---|---|
| Value | %CV | Value | %CV | Value | %CV | Value | %CV |
| 38.4 ± 5.4 | 44 | 38.5 ± 5.5 | 44 | 37.0 ± 5.7 | 47 | 37.2 ± 5.6 | 47 |
| 141.4 ± 8.5 | 13 | 152.6 ± 8.4 | 13 | 163.1 ± 7.2 | 15 | 149.8 ± 7.9 | 12 |
| 1.8 ± 0.0 | 8 | 1.9 ± 0.0 | 7 | 2.0 ± 0.0 | 7 | 1.9 ± 0.0 | 7 |
| 2.1 ± 0.3 | 26 | 2.4 ± 0.2 | 29 | 2.5 ± 0.2 | 29 | 2.5 ± 0.2 | 29 |
| 0.96 ± 0.01 | 3 | 0.96 ± 0.01 | 3 | 0.96 ± 0.01 | 3 | 0.96 ± 0.01 | 3 |
| | | | | | | | |
| −0.0023 | | −0.0017 | | | | −0.0017 | |
| −0.0012 | | −0.0007 | | | | −0.0007 | |
| −0.0029 | | | | | | | |
| | | | | | | | |
| 0.1020 | | | | 0.1080 | | 0.1090 | |
| 0.1150 | | | | 0.0228 | | 0.0402 | |
| 0.0367 | | | | −0.0073 | | −0.0036 | |
| 0.0813 | | | | 0.0544 | | −0.0255 | |
| | | 0.0118 | | | | | |
| | | 0.0184 | | 0.0186 | | 0.0149 | |
| | | 0.0095 | | 0.0120 | | 0.0103 | |
| | | 0.0163 | | 0.0259 | | 0.0206 | |
| | | | | | | | |
| 4,098.3 | | 4,094.0 | | 4,093.3 | | 4,086.9 | |
| 4,134.3 | | 4,128.0 | | 4,129.3 | | 4,126.9 | |
| −0.7 | | −0.4 | | −1.1 | | −0.5 | |
| 16.0 | | 17.2 | | 16.9 | | 16.4 | |

alfentanil.[21] They showed that with decreasing cardiac output, the sum of the intercompartmental clearances of alfentanil decreased in a linear fashion. This is in accordance with our findings for the distribution of propofol. Because cardiac output is determined as stroke volume times heart rate, it is likely that changes in heart rate are correlated with changes in cardiac output.

The primary site of propofol metabolism is the liver. Reported hepatic extraction ratios for propofol vary from 0.79 to 0.92.[22] Because of this high hepatic extraction ratio, changes in hepatic blood flow have an effect on the elimination clearance of propofol, whereas moderate modulations of enzyme activity may not result in a significant alteration of the elimination clearance of propofol. The total blood flow to the liver is approximately 1.5 l/min, or approximately 30% of the cardiac output.[23] An inverse relation was observed between cardiac output and plasma propofol concentrations during constant infusion in anesthetized swine.[24] It is possible that the reduction in heart rate induced by alfentanil, caused a reduction in cardiac output, and thereby a reduction in the hepatosplanchnic blood flow, which may explain the reduced clearance of propofol in the presence of alfentanil. This may explain why, in the final model, the elimination clearance is more readily affected by changes in heart rate than by changes in cardiac output and plasma alfentanil concentration. In this 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 ($R^2 = 0.74$).[25] Still, it is possible that a difference in cardiac output was induced by alfentanil but was too small to be detected by the thoracic bioimpedance method, whereas the difference in heart rate induced by alfentanil was more accurately detected (table 1).

The importance of hepatosplanchnic blood flow on propofol pharmacokinetics has been stressed by Leslie *et al.*[26] They found that during mild hypothermia (34°C), blood propofol concentrations were 28% higher on average compared with normothermia. Their data were best described by a population pharmacokinetic model with hepatic blood flow as a covariate affecting elimination clearance ($Cl_1$). Similarly, hypoxia induced reduction in cardiac output and total hepatic blood flow in rabbits resulted in an accumulation of propofol in blood and a reduced propofol clearance.[27] In addition, mean hepatic blood flow decreased by 17% during propofol anesthesia in mechanically ventilated sheep[28] and induced a marked decrease in splanchnic perfusion in dogs.[29]

In the final model, cardiac output was included as a covariate on $V_1$. When cardiac output decreases from 10 to 5.1 l/min, $V_1$ decreases from 56 to 33 l. In a sheep model, low cardiac output leads to higher peak concentrations after bolus injection because of slower drug–blood mixing.[30] Kazama *et al.*[31] found that hepatic blood flow was a significant predictor of induction dose in a multiple regression model.

Because plasma alfentanil concentration was still included as a covariate on $Cl_1$ and $V_2$ in the final model, the

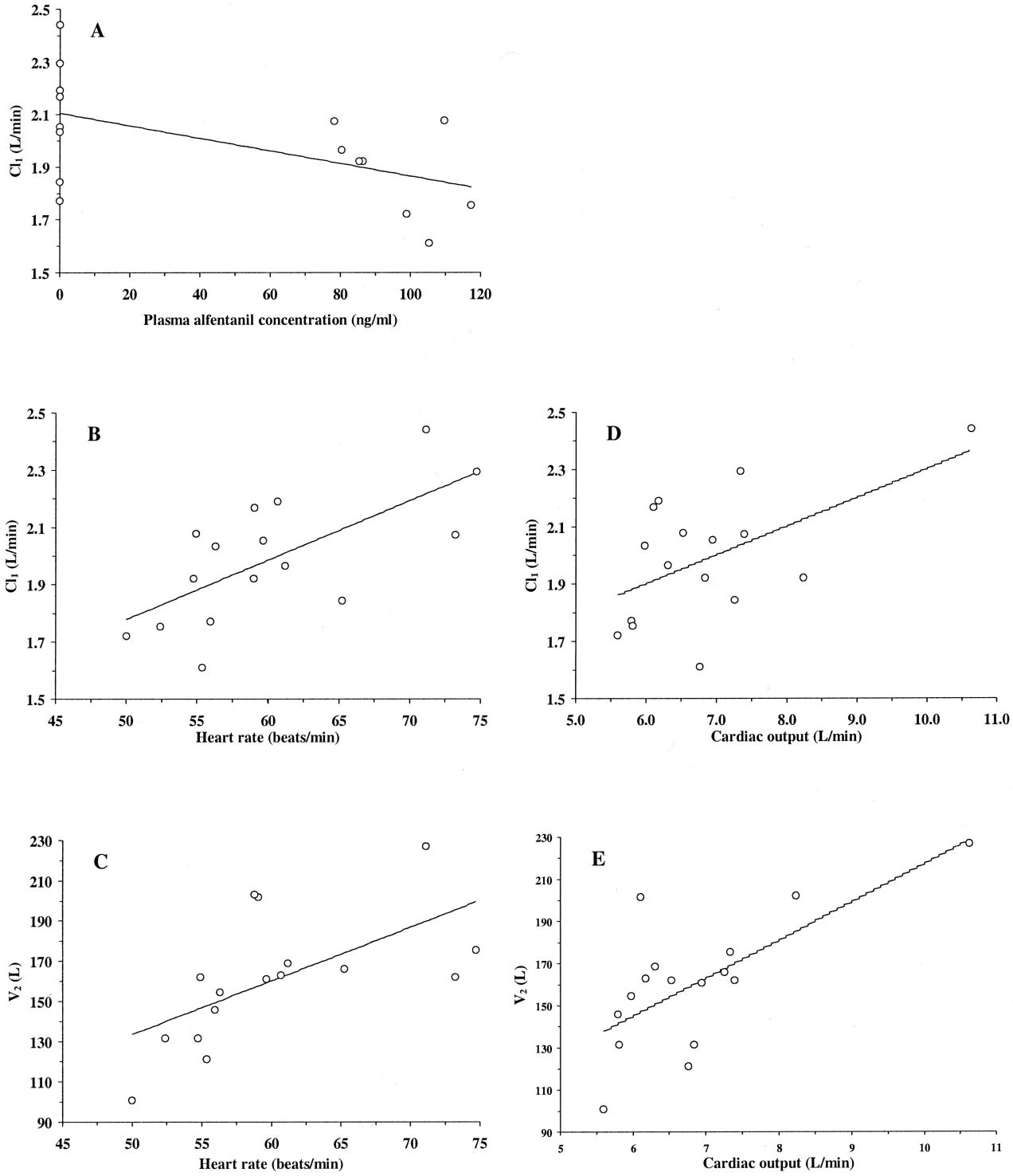


**Fig. 3. Individual Bayesian estimates (*open circles*) of the elimination clearance ($Cl_1$), distribution clearance ($Cl_2$), and the peripheral volume of distribution ($V_2$), obtained from the model, without covariates, as functions of plasma alfentanil concentration (*A*), heart rate (*B* and *C*), and cardiac output (*D* and *E*). The linear relation between plasma alfentanil concentration, heart rate, or cardiac output and $Cl_1$ or $V_2$ (*lines*) were estimated by linear regression (coefficients not presented).**

added interindividual variability of these pharmacokinetic parameters of propofol, introduced by the combined administration with alfentanil, cannot be explained by the variability in cardiac output and heart rate alone.

*Computer Simulations*

Computer simulations of the propofol infusion scheme used in this study, based on the pharmacokinetic model with the plasma alfentanil concentration as the only covariate (table 2, second column), showed that the

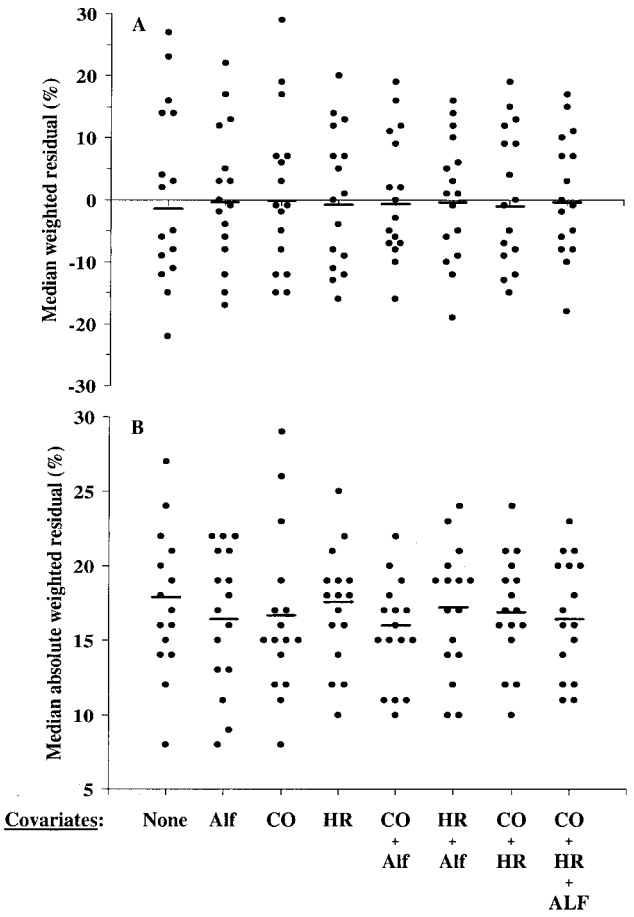


**Fig. 4. Individual median weighted residuals (*A*) and median absolute weighted residuals (*B*) determined for all pharmacokinetic models displayed in table 2. The solid lines are the population median weighted residuals (*A*) and median absolute weighted residuals (*B*). Note that with each reduction in the Akaike information-theoretic criterion of the model, the range of the individual median weighted residual and median absolute weighted residual values decreases. Alf = alfentanil; CO = cardiac output; HR = heart rate.**

predicted mean difference in blood propofol concentration between sessions A and B during propofol infusion was 17%. After stopping the infusion, the difference in blood propofol concentration between sessions A and B ranged from 10% to 25%.

Although the context-sensitive half-time of propofol is increased by up to 2 min for durations of infusion up to 90 min during combined infusion with alfentanil, this increase is too small to be clinically relevant. However, the recovery may be delayed significantly more than suggested by the minimal increase in the context-sensitive half-time, simply because blood propofol concentrations at the end of the infusion are higher in the presence of alfentanil than in the absence of alfentanil (fig. 6).

Of the hemodynamic parameters (cardiac output and heart rate) that were shown to affect the pharmacokinetics of propofol, only the heart rate is generally available in routine clinical practice. Therefore, we further explored the role of the heart rate. Computer simulations showed that a frequently used propofol infusion scheme[32] (2 mg/kg intravenous propofol, administered in 30 s, followed by 12 mg · kg$^{-1}$ · h$^{-1}$ for 15 min, 10 mg · kg$^{-1}$ · h$^{-1}$ for 15 min, and 8 mg · kg$^{-1}$ · h$^{-1}$ for 30 min) in the presence of heart rates of 50, 60, and 70 beats/min, using the pharmacokinetic model with heart rate incorporated as a single covariate, resulted in mean blood propofol concentrations of 3.6, 3.1, and 2.7 μg/ml, respectively, during the infusion (fig. 8). Tachycardia, induced by perioperative stress, and bradycardia, induced by β-adrenoceptor[33] antagonists, may thus have significant effects on the propofol dose–concentration

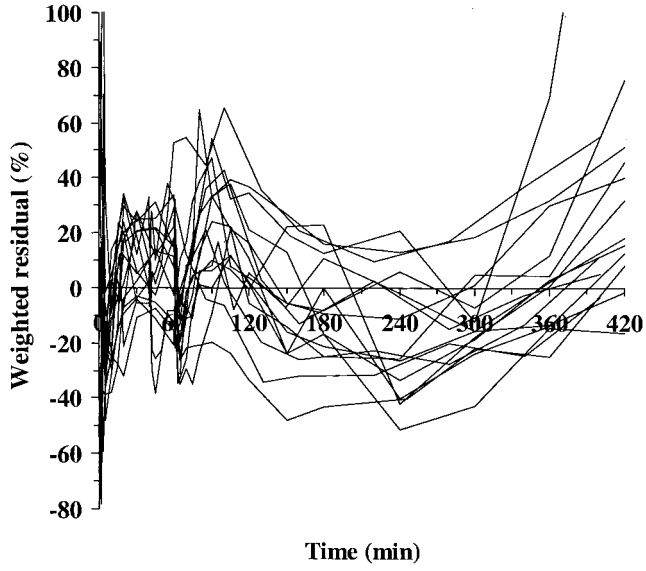


**Fig. 5. Weighted residuals plotted *versus* time, calculated for the model with plasma alfentanil, cardiac output, and heart rate incorporated as covariates (table 2).**

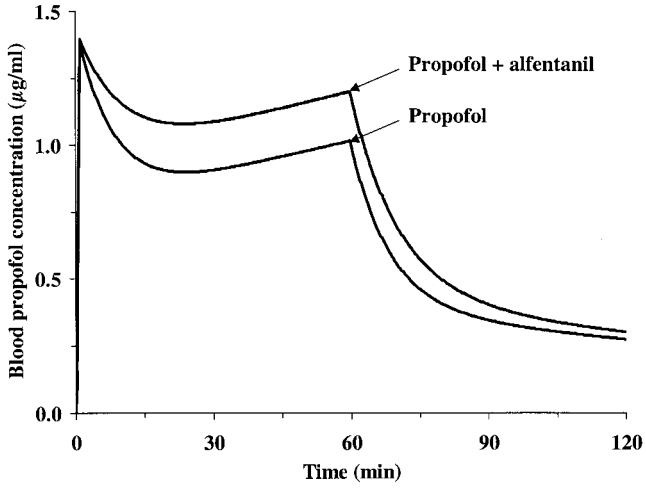


**Fig. 6. Computer simulation of the blood propofol concentration in the presence and absence of a plasma alfentanil concentration of 80 ng/ml, with the infusion scheme used in this study (1 mg/kg intravenous propofol, administered in 1 min, followed by 3 mg · kg$^{-1}$ · h$^{-1}$ for 59 min), using the pharmacokinetic model with plasma alfentanil concentration incorporated as the only covariate (table 2).**

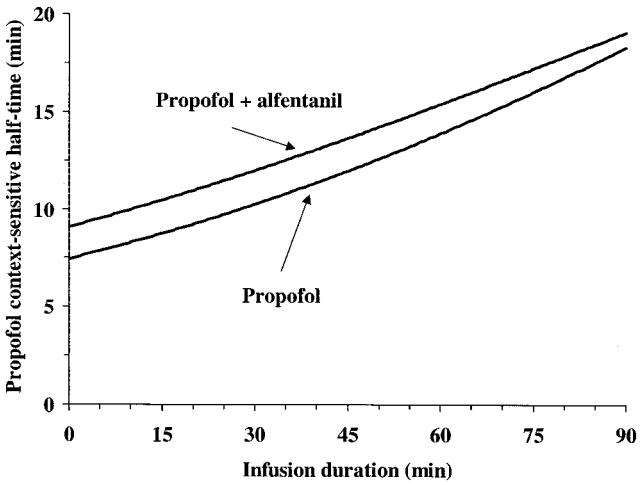


**Fig. 7. Context-sensitive half-times of propofol *versus* infusion duration in the presence and absence of an alfentanil target-controlled infusion with a target concentration of 92.7 ng/ml, using the pharmacokinetic model with alfentanil incorporated as the only covariate, for infusion durations up to 90 min (table 2).**

relation, thereby affecting the dose–effect relation of propofol. Similarly, a study investigating propofol pharmacokinetics in hyperthyroid and euthyroid patients showed a twofold or threefold increase in propofol clearance in hyperthyroid patients.[34] In patients with severe hyperthyroidism, cardiac output can be twice that of euthyroid patients.[35]

Bradycardia induced by the other opioids, fentanyl, sufentanil, and remifentanil, may reduce the clearance of propofol in a manner similar to that of alfentanil and may thereby increase the propofol concentration.

In conclusion, this study shows that when propofol is administered in combination with alfentanil, blood propofol concentrations are 17% higher than in the absence of alfentanil. Alfentanil decreases the elimination clearance, the distribution clearance, and the peripheral volume of distribution of propofol. The inclusion of cardiac output and heart rate as covariates resulted in an improved model compared with the model with the plasma alfentanil concentration as the only covariate. This illustrates that cardiac output and heart rate thus have an important influence on the pharmacokinetics of propofol. However, the effect of alfentanil on the pharmacokinetics of propofol cannot be explained completely by hemodynamic changes because the final model still contains the plasma alfentanil concentration as a covariate, in addition to cardiac output and heart rate.

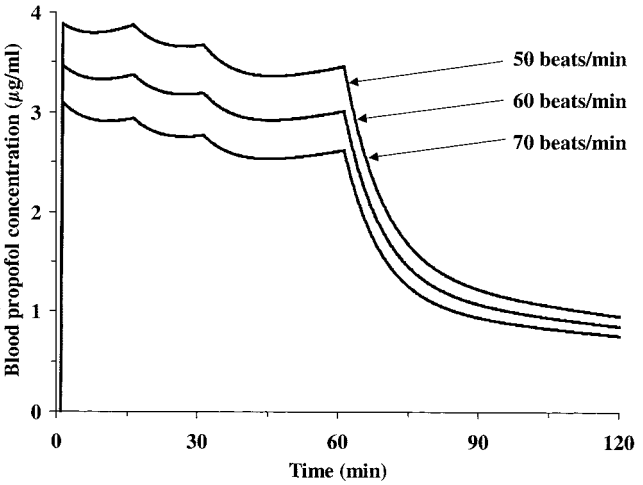


**Fig. 8. Computer simulation of the blood propofol concentration with a frequently used infusion scheme[31] (2 mg/kg intravenous propofol, administered in 30 s, followed by 12 mg · kg$^{-1}$ · h$^{-1}$ for 15 min, 10 mg · kg$^{-1}$ · h$^{-1}$ for 15 min, and 8 mg · kg$^{-1}$ · h$^{-1}$ for 30 min) in the presence of heart rates of 50, 60, and 70 beats/min, using the pharmacokinetic model with heart rate incorporated as a single covariate (table 2).**

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