The Influence of Age on Propofol Pharmacodynamics

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Background: The authors studied the influence of age on the pharmacodynamics of propofol, including characterization of the relationship between plasma concentration and the time course of drug effect.

Methods: The authors evaluated healthy volunteers aged 25–81 yr. A bolus dose (2 mg/kg or 1 mg/kg in persons older than 65 yr) and an infusion (25, 50, 100, or 200 µg·kg⁻¹·min⁻¹) of the older or the new (containing EDTA) formulation of propofol were given on each of two different study days. The propofol concentration was determined in frequent arterial samples. The electroencephalogram (EEG) was used to measure drug effect. A statistical technique called semilinear canonical correlation was used to select components of the EEG power spectrum that correlated optimally with the effect-site concentration. The effect-site concentration was related to drug effect with a biphatic pharmacodynamic model. The plasma effect-site equilibration rate constant was estimated parametrically. Estimates of this rate constant were validated by comparing the predicted time of peak effect with the time of peak EEG effect. The probability of being asleep, as a function of age, was determined from steady state concentrations after 60 min of propofol infusion.

Results: Twenty-four volunteers completed the study. Three parameters of the biphasic pharmacodynamic model were correlated linearly with age. The plasma effect-site equilibration rate constant was 0.456 min⁻¹. The predicted time to peak effect after bolus injection ranging was 1.7 min. The time to peak effect assessed visually was 1.6 min (range, 1–2.4 min). The steady state observations showed increasing sensitivity to propofol in elderly patients, with Cₚ₅₀ values for loss of consciousness of 2.35, 1.8, and 1.25 µg/ml in volunteers who were 25, 50, and 75 yr old, respectively.

Conclusions: Semilinear canonical correlation defined a new measure of propofol effect on the EEG, the canonical univariate parameter for propofol. Using this parameter, propofol plasma effect-site equilibration is faster than previously reported. This fast onset was confirmed by inspection of the EEG data. Elderly patients are more sensitive to the hypnotic and EEG effects of propofol than are younger persons. (Key words: Convolution; covariates; effect site; electroencephalogram; intravenous anesthetics; modeling; population; semilinear canonical correlation.)

THE dose requirement of many hypnotic and analgesic drugs used in anesthesia is reduced in elderly persons.1–3 This can be explained by age-related changes in pharmacokinetics, pharmacodynamics, or both. Recently, we showed that the pharmacokinetics of propofol change with age.4 The purpose of this analysis was to study the influence of age on the pharmacodynamics of propofol. Specifically, we wanted to characterize the influence of age on propofol potency and on the time course of plasma effect-site equilibration. As in previous studies,2,5–7 we used the EEG as a sensitive and continuous measure of drug effect.

There is only one published value for the plasma effect-site equilibration rate constant (kₑₛₑ) for propofol in the peer-reviewed literature, which was reported by Billard et al.8 as an incidental finding in a study comparing different EEG measures of drug effect. Accordingly, one purpose of the current study was to have a carefully
developed \( k_e \) that can be used to predict effect-site concentrations in the clinical setting when combined with an appropriate pharmacokinetic model.

**Methods**

**Clinical Protocol**

After we received approval for the study protocol from the Stanford Institutional Review Board, we enrolled 25 healthy volunteers into the study. One person dropped out because of depression. This person was replaced in the age- and dose-stratified design and was not included in the analysis. The study population and the study design are described in a companion article that reports the influence of age on the pharmacokinetics of propofol.²

For this randomized, double-blinded, two-period, crossover trial, the participants were stratified into three age groups of eight persons each: 18–34 yr, 35–65 yr, and more than 65 yr. Each volunteer was studied twice and received propofol (Zeneca Pharmaceuticals Group, Wilmington, DE) without EDTA (the commercially available formulation of propofol in the United States before July 1996) or propofol with EDTA (the commercially available formulation of propofol in the United States after July 1996) in each study session. All volunteers received a manually delivered bolus over a median time of 18 s (range, 13–24 s; individual times were not correlated with age). Volunteers aged 65 yr and younger received a bolus dose of 2 mg/kg. Volunteers older than 65 yr received a smaller bolus of 1 mg/kg because of safety concerns. One hour after the bolus dose, a 60-min infusion of propofol was administered. The infusion rate was assigned randomly to 25, 50, 100, or 200 \( \mu \)g \( \cdot \) kg\(^{-1}\) \( \cdot \) min\(^{-1}\), with two volunteers in each age group assigned to each infusion rate. Arterial blood samples were taken at 0, 1, 2, 4, 8, 16, 30, 60, 62, 64, 68, 76, 90, 120, 122, 124, 128, 136, 150, 180, 240, 300, and 600 min during each study session.

To measure the electroencephalographic (EEG) response, gold cup electrodes were placed over Cz, FP3, FP4, P3, and P4 according to the international 10/20 system. After we gently rubbed the scalp with an abrasive gel (Omniprep; D.O. Weaver Co., Aurora, CO), the electrodes were fixed to the skin with a sticky electrode cream (Grass EC2; AstroMed, West Warwick, RI). The electrodes were manipulated until the impedance was less than 1,500 \( \Omega \). The volunteers were asked to lie quietly with closed eyes for 5 min of baseline recording. The EEG was digitized at 128-Hz, 12-bit resolution and stored on a computer hard disk for subsequent processing.

**Sleep Duration Analysis**

At the conclusion of the baseline recordings, the volunteers received the bolus injection. All times are referenced to the beginning of the bolus injection. The times of loss of consciousness (LOC) and return of consciousness (ROC) were recorded. Consciousness was assessed every 10 s by asking the volunteers to open their eyes. The sleep duration after the bolus injection was calculated as the time of ROC minus the time of LOC. A correlation between sleep duration and age was sought by linear correlation analysis. The statistical significance of the regression was tested using the F statistic. A \( P \) value of 0.05 was considered significant. The one volunteer who did not fall asleep after the bolus was excluded from this analysis (see the Results section). In addition, the volunteers older than 65 yr were excluded from this analysis because the protocol mandated a reduced dose in these persons (1 mg/kg), precluding direct comparison.

**Electroencephalographic Pharmacodynamic Analysis**

**Signal Processing—Semilinear Canonical Correlation.** Median frequency, activity in specific frequency bands, and the bispectral index have been used as EEG measures of propofol drug effect.⁸⁻¹¹ With these techniques, the EEG response to propofol is generally biphasic,¹²,¹³ reflecting an initial activation followed by profound depression of the EEG. To identify potentially subtle differences in the time course of EEG effect between young and elderly volunteers, we used semilinear canonical correlation to extract those components from the EEG power spectrum that best correlated with the time course of the effect-site concentration.†† This method has been applied successfully to the EEG effects of opioids and midazolam.⁷⁻¹⁴,¹⁵

The method can be summarized as follows. Fourier analysis transformed the digitized raw EEG from the time domain into the frequency domain in epochs of 2 s each from baseline through 20 min after the end of the infu-
sion. Frequencies greater than 30 Hz were discarded, and the resulting EEG power spectrum from 0 to 30 Hz was divided into 10 frequency bins of 3 Hz each. The logarithms of the power in each 3-Hz bin were averaged over 50 s and entered the semilinear canonical correlation analysis described in the appendix. Briefly, each of the 10 bins is multiplied by a weighting factor, and the sum of the 10 weighted bins is the "optimal" (as defined by semilinear canonical correlation) measure of drug effect. The 10 weighting factors are estimated concurrently with the other pharmacodynamic parameters. The resulting measure of drug effect is called the "canonical univariate parameter" (CUP) for propofol.

We also calculated the CUP_{propofol} for the first 10 min after the bolus dose administration from the logarithms of the power in each 3-Hz bin without averaging. From this 2 s resolution effect measure, the time of maximal EEG effect after the bolus was determined. The time at the trough after the initial activation was considered as the time of the peak effect-site concentration. This estimation was performed by visually inspecting each volunteer's EEG data over the first 10 min after bolus injection.

The Electroencephalographic Pharmacodynamic Model

The EEG pharmacodynamic model consists of two $E_{\text{max}}$ models that describe the activation and depression of the EEG with increasing propofol concentrations. At the time of peak activation, the response description moves from the activation model to the depression model. This model is described by the following parameters. The subscript A indicates activation, and the subscript D indicates depression (fig. 1).

\[
\begin{align*}
E_{0,A} &= \text{Baseline EEG and the starting point for the activation model.} \\
E_{\text{max},A} &= \text{Maximal EEG effect possible from the activation model. This value is never reached because the model changes from activation to depression before } E_{\text{max},A} \text{ is reached.} \\
C_{50,A} &= \text{The effect-site propofol concentration associated with 50% of peak activation (} E_{\text{max},A} \text{).} \\
\gamma_A &= \text{The steepness of the concentration versus response relation for EEG activation.} \\
C_{\text{peak}} &= \text{The effect-site propofol concentration at peak activation.} \\
E_{0,D} &= \text{The peak activation at the point of transition from the activation model to the depression model. This becomes the starting value of the depression model.} \\
E_{\text{max},D} &= \text{The maximum depression from the point of peak activation (} E_{0,D} \text{).} \\
C_{50,D} &= \text{The effect-site propofol concentration associated with 50% depression from peak activation.} \\
\gamma_D &= \text{The steepness of the concentration versus response relation for EEG depression.}
\end{align*}
\]
k_{e0} = \text{The rate constant for equilibration between the plasma and the effect site.}

The parameters F_{0,A} and E_{max,A} enter the model linearly, and thus the optimal value under ordinary least-squares regression can be calculated directly. The parameter F_{0,D} can be calculated from C_{max} and the parameters of the activation model. Therefore, using ordinary least-squares regression analysis, for each study we estimated the values of C_{50,A}, \gamma_A, C_{peak}, C_{50,D}, \gamma_D, and E_{max,D} and k_{e0}. For this we had to estimate 536 parameters (7 parameters \times 48 studies). The 10 weighting factors that define the canonical univariate measure of propofol drug effect were estimated in the same regression for all studies (a pooled technique as described in appendix 1). The resulting 536 parameters of the model were optimized simultaneously using an extended implementation of the "Solver" function (Frontline Systems, Incline Village, NV) using Excel (Microsoft, Redmond, WA). The performance of the model was determined using the coefficient of multiple determination (R^2), as described in appendix 1.

We explored the pharmacodynamic parameters for age effects using linear models. The slope of the regression curve was tested for significance using the F statistic. A P value of 0.05 was considered significant.

Estimation of the Effect-site Concentration

The effect site was assumed to be linked to the plasma compartment by a traditional first-order process, so that the effect-site concentrations over time could be calculated as the convolution of the plasma concentrations over time, C_p(t), with the disposition function of the effect site, k_{e0} e^{-k_{e0} t}. The estimate of k_{e0} depends on the representation of C_p(t), the plasma concentrations over time. We represented the plasma concentrations over time in two different ways. This reflects the different goals at different stages in the analysis.

First, for the semilinear canonical correlation, described previously, our primary goals were to determine a statistically optimal EEG measure of propofol drug effect (the CUP_{propofol}) and the influence of age on propofol pharmacodynamics. Classical mamilillary pharmacokinetic models assume instantaneous mixing, which is not a valid assumption. Assuming instantaneous mixing may introduce bias at the early time points. To prevent this potential artifact from affecting either our modeling of the CUP_{propofol} or the influence of age on propofol pharmacodynamics, we used the measured plasma drug concentrations as the input function, C_p(t).

In this "connect-the-dots" representation of the plasma concentrations, the concentrations were modeled as linearly increasing and log-linearly decreasing. Effect-site concentrations were calculated as the numeric convolution of the measured concentrations over time with the disposition function of the effect site.

Second, the connect-the-dots representation of C_p(t) is nearly useless outside of this study. Most applications of pharmacokinetics require that C_p(t) be represented by a parametric model. To permit an estimation of the effect-site concentrations over time when C_p(t) is represented by the pharmacokinetic model in our companion article, \textsuperscript{1} we also estimated k_{e0}, assuming that the plasma concentrations over time were those predicted by our covariate-adjusted pharmacokinetic model. The analysis estimated k_{e0} and the other pharmacodynamic parameters. The EEG measure of drug effect (CUP_{propofol}) was fixed at the "optimal" values determined using the connect-the-dots representation of the plasma pharmacokinetics.

To quickly summarize: k_{e0} is part of a vector of pharmacokinetic parameters. We first estimated k_{e0} using measured plasma propofol concentrations and model-independent (connect-the-dots) numeric convolution to develop an optimal EEG measure of propofol drug effect and optimal estimates of the propofol concentration versus effect measurement relation. Then we estimated k_{e0} again for use with the pharmacokinetic model published in our companion article.\textsuperscript{1}

Loss of Consciousness Pharmacodynamic Analysis

During a constant infusion, the propofol plasma concentration increases rapidly at the beginning. Over time the rate of increase in concentration becomes smaller. Our pharmacokinetic model predicts that the concentration should increase by less than 5% between 50 min of infusion and 60 min. Because of its rapid plasma effect-site equilibration, the propofol concentration at the end of a 60-min infusion can be assumed to be equilibrated with the effect-site concentration. We correlated the measured plasma propofol concentration drawn immediately before the infusion was stopped at 60 min with the probability of being asleep at that moment, using the model

\[ P_{\text{asleep}} = \frac{C_p}{C_p + C_{50}} (\text{age-independent model}). \]

The likelihood, \textit{L}, for the observed response, \textit{R} (awake: \textit{R} = 0; asleep: \textit{R} = 1), is expressed by the formula

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L = P_{\text{asleep}}^R \cdot (1 - P_{\text{asleep}})^{1-R}

and the log of the joint likelihood for all 48 observations, which is the objective function to be minimized for estimating the parameters \( g \) and \( C_{50} \), is described by the formula

\[
\text{LL} = \sum_{i=1}^{48} R_i \cdot \log (P_{\text{asleep}}) + (1 - R_i) \cdot \log (1 - P_{\text{asleep}})
\]

where \( R_i \) denotes the observed response (being asleep or being awake) in the \( i \)th participant. The age-dependent concentration at which 50% of the participants are asleep \( (C_{50}) \) was calculated by applying the formula

\[ C_{50} = a + b \cdot \text{age} \]

and so the age effect was modeled using the following equation:

\[
P_{\text{asleep}} = \frac{C^7}{C^7 + (a + b \cdot \text{age})^7} \quad \text{(age-dependent model)}
\]

where the parameters \( g, a, \) and \( b \) are estimated.

The influence of the propofol formulation was explored using the equation

\[ P_{\text{asleep}} = \frac{C^7}{C^7 + (x \cdot \text{PREP} + y \cdot (1 - \text{PREP}))^7} \]

PREP was coded as 0 or 1, depending on the presence or absence of EDTA in the formulation, and the parameters \( x \) and \( y \) are estimated iteratively. The significance of additional parameters was tested using the likelihood ratio test. A \( P \) value of 0.05 was considered significant.

The influence of the preparation on two measured clinical endpoints, time to LOC and sleep duration, were compared using a paired \( t \) test. A \( P \) value of 0.05 was considered significant.

**Results**

**Clinical Protocol**

Table 1 summarizes the demographic data of the volunteers. All 24 participants who completed both study sessions were included in the analysis. One of them, who was aged 27 yr, did not fall asleep after the bolus dose in either study session. He was not included in the analyses related to sleep duration, but he was included in all other analyses. The EEG data from 5 min before the bolus dose to 20 min after the end of the infusion were analyzed, except in one volunteer whose EEG electrodes were dislodged 10 min after the end of the infusion.
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Table 1. Study Population

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<th>Infrate (µg · kg⁻¹ · min⁻¹)</th>
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Sleep Duration Analysis

Figure 2 depicts the relation between age and sleep duration after the bolus dose (upper graph) in volunteers younger than 65 yr. Although the data are limited to participants younger than 65 yr, the regression of age versus sleep duration (upper graph) and age versus time to ROC (lower graph) were both significant at $P < 0.0001$. The time to LOC (middle graph) did not vary with age. Figure 2 shows that the correlation between age and duration of sleep results from a longer time to ROC and not from an earlier LOC. Figure 2 does not establish the mechanism for the increased sensitivity with increasing age, which could be caused by the documented pharmacokinetic changes in the elderly, increased pharmacodynamic sensitivity, or both.

Electroencephalographic Pharmacodynamic Analysis

Table 2 shows the semilinear canonical coefficients of the EEG effect. Table 3 shows the parameters of the biphasic pharmacodynamic model developed using the connect-the-dots representation of plasma concentration. The biphasic pharmacodynamic model accurately described the shape of the concentration versus effect relation. The upper panel of figure 3 shows a participant with a biphasic response fitted using this model. The lower panel of figure 3 shows another participant with only an activation phase. Figure 4 shows the full time course of measured and fitted EEG effect for a volunteer, revealing a biphasic response during the infusion.

Figure 5 shows the distribution of $R^2$ values and pharmacodynamic parameters for the EEG analysis. Figure 5 indicates that there was no pattern suggesting that low $R^2$ values were associated with estimates of $k_o$ that were greater or less than average estimates. Because many of

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Fig. 2. Sleep duration, time to loss of consciousness, and time to return of consciousness as a function of age in those volunteers 65 yr and younger after a propofol bolus dose of 2 mg·kg. The sleep duration is the time to return of consciousness (lower panel) minus the time of loss of consciousness (middle panel). Volunteers older than 65 yr received a reduced bolus dose because of safety concerns, and for this reason they were not included here. The participant who did not fall asleep after the bolus dose was not included in this part of the analysis.
the volunteers who received 25 μg · kg⁻¹ · min⁻¹ had little EEG effect during the infusion, the R² values in these persons were low, expressing the low signal noise ratio during the infusion. In these persons, the pharmacodynamic parameters were determined primarily by the bolus response. The parameters gₓ and Cₓ₀,A and Cₓ₀,D showed less variability than the other parameters did.

Cₓ₀,A, γₓ,A, and γₓ,D were correlated with age. These correlations are summarized in figure 6. The probability that slope (estimated using linear regression) would be equal to 0 (null hypothesis) was P = 0.017 for Cₓ₀,A, P = 0.035 for γₓ,A, and P = 0.02 for γₓ,D. This result shows that the EEG activation in older persons occurs at lower concentrations but also that the transition from no effect to maximal activation is more gradual because the effect-site–concentration-effect relation is less steep. None of the parameters were correlated with the preparation of propofol used (with or without EDTA). Table 3 also shows the age-adjusted models for Cₓ₀,A, γₓ,A, and γₓ,D. The median value of kₓ₀ with the connect-the-dots model of plasma concentration (i.e., numeric convolution) used in the EEG pharmacodynamic regression was 0.316 min⁻¹ (table 4). This was associated with a median time of peak effect-site concentration, tₓ₀,peaks, of 1.96 min after bolus injection. The kₓ₀ value calculated by representing the plasma concentrations with the covariate-adjusted pharmacokinetic parameters from our companion article⁴ was 0.456 min⁻¹, with a corresponding tₓ₀,peaks of 1.69 min.

**Table 2. Coefficients Defining the Canonical Univariate Parameter** (CUP.propofol) **Obtained Using the “Connect-the-dots” Pharmacokinetics**

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<th>Frequency Bin (Hz)</th>
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**Table 3. Pharmacodynamic Parameters**

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<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Cₓ₀,A</td>
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<tr>
<td>γₓ,A (age adjusted)</td>
<td>3.7 × 0.017 × AGE</td>
<td>—</td>
</tr>
<tr>
<td>γₓ,D (age adjusted)</td>
<td>2.3 × 0.011 × AGE</td>
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</tbody>
</table>

AGE = age in years.

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Fig. 3. The effect-site concentration versus the electroencephalogram effect relation from two different volunteers show a biphasic (upper panel) and a monophasic (lower panel) response. In the volunteer with the biphasic response, the electroencephalogram reached a peak at about 1.3 mg/ml. In the other volunteer, the effect increased continuously to an effect-site concentration of 3.3 mg/ml, the highest effect-site concentration in this volunteer.

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Loss-of-consciousness Pharmacodynamic Analysis

The measured plasma concentration at the end of the infusion period ranged from 0.36 mg/ml to 6.8 mg/ml.
AGE AND PROPOFOL PHARMACODYNAMICS

Fig. 4. The observed and predicted effect over time in one volunteer with a biphasic response. An activation (A) and depression (D) phase is apparent when the effect-site concentration is increasing. Reactivation of the electroencephalogram (RA) and final recovery from drug effect (R) occurs when the effect-site concentration is decreasing.

with a median value of 1.9 mg/ml. The $C_{50}$ for conscious-unconscious was 1.68 µg/ml, and $\gamma$ was 3.79. The standard errors were 0.196 and 1.58 for $C_{50}$ and $\gamma$, respectively. Using age as a covariate for $C_{50}$ improved the fit significantly based on the likelihood ratio test ($P = 0.027$). The final model with age was expressed using the formula

$$P_{\text{asleep}} = \frac{C^{4.29}}{C^{4.29} + (2.9 - 0.022 \cdot \text{age})^{4.29}}$$

where $P_{\text{asleep}}$ is the probability that the volunteer was unconscious at the end of the infusion, and $C$ is the concentration at the end of the infusion. In this model, $C_{50}$ was linearly dependent on age and was calculated as: $C_{50} = 2.9 - 0.022 \cdot \text{age}$. Thus, the $C_{50}$ in 25-, 50-, and 75-yr-old volunteers would be 2.35, 1.8, and 1.25 µg/ml, respectively. The standard errors of the parameters $\gamma$, the $C_{50}$ intercept, and the $C_{50}$ slope were 1.77, 0.48, and 0.0093, respectively. The data, together with the fitted model, are shown in figure 7. When the $C_{50}$ was modeled as being different for the two preparations, the likelihood did not improve, suggesting that the presence of EDTA does not alter the potency of propofol.

Model Validation

Table 4 documents the values of $k_{eq}$ and the times to peak effect-site concentration after bolus injection based on two representations of the plasma concentrations over time. The value of $k_{eq}$ estimated using the connect-the-dots representation of the plasma propofol concentration was 0.316 min$^{-1}$, with a corresponding $t_{\text{peak}}$ of 1.96 min, which is reasonably close to the value for $t_{\text{peak}}$ obtained by visual inspection. Because the representation of the plasma concentration used to develop this value of $k_{eq}$ cannot be adapted easily to other purposes, this particular value of $k_{eq}$ has little use outside of this analysis. Its validation in this step is solely intended to indirectly validate the $CUP_{\text{propofol}}$ as a measure of drug

---

Fig. 5. This "parallel plot" shows the association between $R^2$ and the plasma effect-site equilibration rate constant ($k_{eq}$) and the other pharmacodynamic parameters. The x axis represents the proportional value of each estimate to the smallest and largest values, which define the left and right edges, respectively. The $k_{eq}$ estimates are not biased by high or low $R^2$ values. $R^2$ represents the signal-to-noise ratio. The parameters that are significantly correlated with age have less variability than do the others.

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Fig. 6. The relation between age and the three pharmacodynamic parameters with a regression slope significantly different from 0 is shown. The smaller $C_{50a}$ values in the elderly indicate a higher sensitivity of this age group. In addition, a smaller $g_s$ is responsible for a fast transition from no activation to maximal activation.

effect, because both the $k_{co}$ and the $CUP_{propofol}$ were developed using the connect-the-dots representation of plasma concentration.

Table 4 also shows the values of $k_{co}$ that should be used with the propofol pharmacokinetics described in our companion article$^4$ to produce the most accurate representation of the time course of drug effect. With the pharmacokinetic model from our companion study and the $k_{co}$ value of 0.456 min$^{-1}$, the median time to peak effect-site concentration (1.69 min) matches the observed time to peak effect (1.6 min) very well. Figure 8 shows the correlation between age and the visually measured times to peak effect-site concentration (solid line). A tendency for an increased time to peak effect in the elderly was observed, but the correlation was not significant. Figure 8 also shows the time to peak effect with the $k_{co}$ of 0.456 min$^{-1}$ and the pharmacokinetics reported by Schnider et al.$^4$ (dashed line). The positive slope of the predictions using the pharmacokinetics reported by Schnider et al. is a consequence of the age-dependent pharmacokinetics.

Figure 9 shows the relation between the measured sleep duration and the sleep duration predicted by the linked pharmacokinetic–pharmacodynamic model. The line of identity in figure 9 permits indicates the agreement of measured and predicted values. The bias, calculated as the median of the difference between the observed and predicted sleep duration, was −0.72 min without correction of the sleep threshold for age and −0.56 min when the sleep threshold was age dependent according to the analysis of the LOC data. The median of the absolute difference between observed and predicted sleep duration, which is a measure of the accuracy, was

Table 4. Median $k_{co}$ Values and Median Times to Peak Effect-site Concentration after Bolus Injection

<table>
<thead>
<tr>
<th>Estimation Method</th>
<th>$k_{co}$ (min$^{-1}$)</th>
<th>$t_{1/2,k_{co}}$ (min)</th>
<th>$t_{peak}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Connect-the-dots&quot; for EEG pharmacodynamic analysis</td>
<td>0.316</td>
<td>2.2</td>
<td>1.96</td>
</tr>
<tr>
<td>With pharmacokinetics described by Schnider</td>
<td>0.459</td>
<td>1.5</td>
<td>1.69</td>
</tr>
<tr>
<td>Visual inspection of EEG data</td>
<td>—</td>
<td>—</td>
<td>1.6</td>
</tr>
</tbody>
</table>

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Fig. 7. The fit of the logistic regression model is shown. The solid line represents the fit through the data with the age-independent model. The dotted lines are the fits predicted by the age-adjusted regression model for 25-, 50-, and 75-yr-old participants.
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1.4 min with the same sleep threshold and 1.24 min with the age-adjusted sleep threshold. The values for accuracy are not as important here as the values for bias are, because the predictions were based on C_{so} values, which by definition will underestimate 50% of the sleep durations and overestimate 50%. Both accuracy and bias, however, were improved when the sleep threshold was age adjusted.

Our analysis of the effect-site concentrations at LOC and ROC did not reveal any correlation with age or any significant differences between C_{LOC} and C_{ROC}. The mean C_{LOC} and C_{ROC} value was $1.67 \pm 0.09$ (SEM) $\mu$g/ml. The C_{so} for wakefulness, based on the plasma concentration at the end of the infusion, was 1.68 $\mu$g/ml, which is in close agreement with the model for the effect-site concentrations at the times of LOC and ROC.

Discussion

In this study, we determined the influence of age on the pharmacodynamics of propofol, assessed using EEG measures and responsiveness to verbal command. The CUP_{propofol} was our EEG measure of drug effect. The median $R^2$ was 0.48 (range, 0.1–0.95). This compared favorably to the $R^2$ of 0.2 obtained in a preliminary analysis with median frequency. This result is consistent with previous investigations of the performance of CUP applied to opioids and benzodiazepines.

Using the EEG as the measure of drug effect, Homer and Stanski\textsuperscript{18} showed that the pharmacokinetics, but not the pharmacodynamics, of thiopental change with age. Subsequently, Stanski and Maitre\textsuperscript{19} confirmed these findings in a follow-up study. Etomidate also shows age-related pharmacokinetic changes that account for the increased sensitivity to etomidate in the elderly.\textsuperscript{1} However, continuous measurement of EEG median frequency showed no increased brain sensitivity to etomidate with increasing age. An increased sensitivity with age also has

Fig. 8. The correlation between age and the time to peak effect-site concentration. The measured time to peak effect-site concentration shows a tendency of being longer in the elderly. Using the age-adjusted pharmacokinetic parameters of Schidler et al., or the estimation of the k_{on} value and the time to peak effect-site concentration, the correlation is very similar.

Fig. 9. The sleep duration after the bolus dose was calculated using the age-adjusted pharmacokinetic model for all participants. The upper panel shows the results with the population mean C_{so} for all volunteers from the loss-of-consciousness analysis. The lower panel shows the results with the C_{so} adjusted for age. The age correction produced a modest decrease in bias and improvement in accuracy in predicted sleep duration. The straight line indicates unity.

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been reported for midazolam, based on steady-state concentrations.\(^3\)

Opioids show the opposite pattern: The mechanism of increased sensitivity to opioids in the elderly is primarily increased brain sensitivity. When Scott and Stanski\(^20\) measured the opioid effect using the EEG parameter *spectral edge*, the lower dose requirement for fentanyl and alfentanil in their elderly participants could be attributed to increased brain sensitivity. Only minor pharmacokinetic differences were noted between young and elderly participants. A complex age dependency of the pharmacokinetics and the pharmacodynamics was shown for the new esterase-metabolized opioid remifentanil.\(^2\) The pharmacokinetics, the equilibration rate constant between the plasma and the effect site \((k_{e0})\), and brain sensitivity were all age dependent. Simulations indicated that the peak effect-site concentration after bolus injection was unchanged with age, although it was reached later in the elderly. Increased brain sensitivity accounted for the increased sensitivity to a bolus injection of remifentanil in the elderly, whereas a combination of increased brain sensitivity and decreased clearance accounted for the much smaller remifentanil infusion requirement in the elderly.\(^21\)

**Sleep Duration Analysis**

The time to LOC after the bolus dose was not responsible for the longer sleep duration in the elderly. It is possible that after the bolus the initial plasma concentration increases so steeply that it quickly produces an effect-site concentration much greater than the sleep threshold in most of the participants. During the offset of the bolus dose effect, the increased sensitivity to propofol in the elderly is likely responsible for the longer time to ROC, particularly because the pharmacokinetics actually predict a faster initial decrease in the plasma concentration in the elderly.

**Electroencephalographic Pharmacodynamic Analysis**

The EEG is a continuous measure of drug effect. As in previous analyses, we calculated one effect measure every 30 s from the processed EEG. Because we obtained many observations per participant, we performed individual fits rather than using a population approach, such as mixed-effects modeling. With more than 200 data points per volunteer and 13,000 data points in all, it was impractical to approach the estimation process computationally using mixed-effects modeling (such as by NONMEM\(^{\dagger\dagger}\)). In addition, a mixed-effects approach for the semiparametric canonical correlation is not yet available.

In this study, we evaluated the plasma effect-site equilibration time using EEG data. The EEG effect of propofol is biphasic. A pharmacodynamic model other than the classical sigmoidal \(E_{\text{max}}\) model was necessary to describe the biphasic effect-site concentration versus effect relation.

We used the EEG data to calculate the rate of plasma effect-site equilibration. An accurate estimation of the \(k_{e0}\) is necessary for various purposes, such as designing and interpreting clinical trials and predicting effect-site concentrations during computer-controlled drug administration. The half-life for the plasma effect-site equilibration from these data, 1.5 min, is shorter than previously reported half-lives for the plasma effect-site equilibration of propofol. Depending on the effect measure, Billard \textit{et al.}\(^8\) reported \(t_{1/2}\) \(k_{e0}\) values between 2.6 min (obtained with power in the \(\delta\) band) and 3.3 min (using the bispectral index as the measure of drug effect). Schüttrler \textit{et al.}\(^\text{a}\) also reported a \(t_{1/2}\) \(k_{e0}\) value of 2.9 min. Similarly, a \(k_{e0}\) of 0.25 min\(^{-1}\) was incorporated into the computer program STANPUMP, based on preliminary work by Barry Dyck in our laboratory, and has been used experimentally.\(^22\)

The more rapid propofol plasma effect-site equilibration estimated in this study may be caused by the difference in pharmacodynamic models. The traditional model of drug effect is a monophasic sigmoidal \(E_{\text{max}}\) model. Using a biphasic model, we can incorporate the EEG activation and the EEG depression in the model, which allows us to capture the shape of the EEG changes more accurately. In addition, many studies have used \textit{ad hoc} measures of drug effect, such as aperiodic analysis, spectral edge, and median frequency. In this study, we developed a statistically optimal measure of propofol drug effect, possibly permitting better resolution of the time course of drug effect.

Classical mamillary compartmental models of pharmacokinetics assume that the central compartment is well mixed. This is not physiologically correct, and it leads to predictions that a concentration gradient exists between the plasma and the effect site for the first 30 s when, in fact, no such gradient actually exists. For drugs with slow plasma effect-site equilibration, this is unlikely to
bias the estimate of $k_{eq}$. However, if the equilibration is rapid, this misspecification may bias $k_{eq}$ particularly when bolus response data are used. To reduce the potential for misspecification, we calculated $k_{eq}$ using two different models: a connect-the-dots representation of plasma propofol concentration and the pharmacokinetic model for propofol described in our companion article.4

The value of $k_{eq}$ estimated using a convolution of the observed plasma concentrations over time with the disposition function of the effect site cannot be used with parametric pharmacokinetic models, because these models presume different plasma concentrations, particularly during the first 30 s. The model that we therefore recommend from this analysis is the $k_{eq}$ estimated using the pharmacokinetics reported in our companion article.4

The EEG response to propofol is biphasic, with an initial activation phase followed by EEG depression. The biphasic model does not include a single $C_{50}$, but rather has a $C_{50}$ for activation and a $C_{50}$ for EEG depression. We found that $C_{50}$, the measure of potency associated with EEG activation, was significantly and negatively correlated with age, which suggests that age increases the sensitivity of the brain to propofol.

**Loss-of-consciousness Pharmacodynamic Analysis**

Our study design permitted us to determine concentration versus effect relations in both steady state (toward the end of the infusion) and non–steady state conditions. The concentrations toward the end of the infusion spanned a sufficiently wide range that we had well-balanced data for analysis of responsiveness to verbal command. Previously reported values of the concentration necessary for 50% of the participants to be awake range from 1.07 to 4.4 μg/ml.25-27 Our age-independent value of 1.68 μg/ml falls in the lower end of this range. The value likely depends on whether other drugs (e.g., opioids) have been administered concurrently and on the intensity of the stimulus for testing consciousness. We asked volunteers to open their eyes, but we did not otherwise stimulate them to assess mental status, which may explain why our value is relatively low.24

The propofol steady state plasma $C_{50}$ in a 25-yr-old volunteer is twice the $C_{50}$ for a 75-yr-old volunteer. The observed age effect on the propofol steady state plasma $C_{50}$ for being asleep confirms the greater intrinsic sensitivity to propofol in the elderly population. This effect is likely to potentiate the influence of age resulting from pharmacokinetic differences.4 Although the age effect is large, interindividual variability also is large, requiring a careful study design to observe the age-related change in pharmacodynamics.

**Model Validation**

Because of the extensive use of modeling in this analysis, we endeavored to validate the findings of our modeling against “raw” data whenever possible. In particular, we wanted to validate our $k_{eq}$ estimates and our finding of increasing brain sensitivity with age. To validate the different estimates of $k_{eq}$, we compared the predicted times of peak drug effect after bolus injection with the observed time of peak EEG effect. We also evaluated the relationship between age and the nearly steady state plasma concentration associated with LOC. To validate the magnitude of the effect-site concentrations predicted by $k_{eq}$, we compared the predicted effect-site concentrations at the times of LOC and ROC with the nearly steady state plasma concentration at the end of the infusion associated with unconsciousness.

Visual inspection of the EEG over time after bolus injection indicated a median time to peak effect of 1.6 min. This confirms the finding of a rapid $k_{eq}$ half-life. We are confident of this finding, although it differs considerably with the values of $k_{eq}$ estimated in our laboratory by Billard et al.8 and by Dyck (unpublished data), and with the value reported by Schuttler et al.9 Using bispectral analysis as the measure of drug effect, Flaisbon et al.10 reported that the propofol effect peaked 1.8 min after a bolus injection, which is nearly identical to our findings. The observed time of peak effect agrees almost exactly with that predicted using the pharmacokinetics reported by Schneider et al.1 and a $k_{eq}$ value of 0.456 min⁻¹. This leads us to believe that the propofol pharmacokinetics in our companion article are an appropriate representation of the plasma concentrations over time for use with an effect-site model of propofol.

We observed a tendency to longer time to peak effect in the elderly. The same relation was also predicted with the age-adjusted pharmacokinetic parameters. Although this relation between age and time to peak effect was not significant, it matches the clinical observation that the onset of effect after a small bolus is longer in the elderly.

We found that sleep duration was significantly correlated with age. The integrated pharmacokinetic–pharmacodynamic model predicted the sleep duration with reasonable accuracy (median error, 1.24 min) and minimal bias (approximately 34 s). This also suggests that the pharmacokinetic model from our companion article, when combined with a $k_{eq}$ of 0.456 min⁻¹, is reasonably accurate at predicting the time course of the drug effect.
In addition, the improvement of both accuracy and bias after age adjusting the sleep threshold is additional evidence of the age dependence of the propofol pharmacodynamics.

The plasma concentration at the end of the infusion associated with a 50% probability of being asleep was significantly correlated with age, with elderly patients being nearly twice as sensitive to propofol as younger patients are. This confirms the increased sensitivity implied by the relation of \( C_{50,A} \) to age. We did not find an age effect on \( C_{50,D} \), the concentration associated with 50% of EEG depression. However, with this study design, many participants had slow infusions that did not suppress the EEG sufficiently to permit the characterization of \( C_{50,D} \). It is possible that \( C_{50,D} \) is affected by age, but our study design could not identify this change. However, had we given infusions that were rapid enough to explore \( C_{50,D} \) in all our volunteers, we would not have been able to relate the plasma concentrations at the end of the infusion with the probability of being asleep, because all the volunteers would have been unconscious at the end of the infusion.

### Conclusions

We developed a new measure of propofol drug effect on the EEG, the CUP for propofol. This EEG measure is a potentially useful surrogate marker for studying propofol pharmacodynamics. However, we do not propose that the CUP for propofol has clinical utility, as has been shown for the bispectral index.\(^{13}\) Using the CUP, we have estimated the rate of plasma effect-site equilibration for propofol, and we calculated values of \( k_{e0} \) for use with two representations of plasma propofol concentration. Our model indicates faster propofol effect-site equilibration than do previously published reports and faster onset than estimated by J. Barry Dyck, M.D. (unpublished data), and incorporated in the program STAN-PUMP. The faster onset of the propofol drug effect is confirmed by inspection of the EEG data. The value of \( k_{e0} \) that we estimated in this investigation would be appropriate for use with the pharmacokinetic parameters reported by Schneider et al.\(^{4}\) to predict effect-site concentration, as in target-controlled infusions.

We have shown that several indices of brain sensitivity, including the \( C_{50} \) for EEG activation and the steady-state plasma \( C_{50} \) for wakefulness, have increased sensitivity to the propofol drug effect in the elderly. These findings indicate that propofol dosing in the elderly should be reduced for pharmacokinetic, as described in our companion article, and for pharmacodynamic reasons.

The authors thank the late J. Barry Dyck, M.D., for his many years of work on propofol pharmacokinetics and pharmacodynamics.

### References


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**Appendix 1.**

**Calculation of the Effect-site Concentration with Measured Plasma Concentrations**

The concentration at time \( t \) in the interval \( \Delta t = t_{t+1} - t_t \) with a measured concentration of \( C_p(t_t) \) at time \( t_t \), can be expressed by the formula

\[
C_p(t) = C_p(t_t) + t \cdot \left[ \frac{C_p(t_{t+1}) - C_p(t_t)}{t_{t+1} - t_t} \right] \quad \text{when} \quad C_p(t_{t+1}) \geq C_p(t_t)
\]

\[
C_p(t) + e^{t \cdot k_{el} \cdot t_{t+1} + \log(C_p(t_t) / C_p(t_{t+1}))} \quad \text{when} \quad C_p(t_{t+1}) < C_p(t_t).
\]

The effect-site concentration at time \( t \) in the interval is then calculated as

\[
C_p(t) = C_p(t_t) \cdot e^{-t \cdot k_{el} \cdot t_{t+1}} + C_p(t_t) \cdot k_{el} \cdot e^{-t \cdot k_{el} \cdot t_{t+1}}
\]

\( k_{el} \) denotes the plasma–brain equilibration constant and \( C_p \) the effect-site concentration and \( t \) is the convolution operator.

**Semilinar Canonical Correlation**

Standard linear regression relates a dependent variable to a linear combination or weighted sum of independent variables, plus random error \((Y = w_1X_1 + w_2X_2 + \ldots + w_nX_n + \epsilon)\). To minimize the difference between the dependent variable, \( Y \), and the prediction, the weights (\( w \)) on the independent variables (\( X_i \)) are iteratively searched by some objective criterion (e.g., minimum squared error, maximum likelihood, and so forth). If the dependent variable also expressed as a linear combination of individual measures, \( Y \), and the coefficients \( \gamma_1(Y_1 + Y_2 + \ldots + Y_m) \), \( \gamma_2(Y_2 + \ldots + Y_m) \), \( \gamma_3(Y_3 + \ldots + Y_m) \), \( \ldots \), \( \gamma_m(Y_m) \), the difference between \( Y = Y_1 + Y_2 + \ldots + Y_m \) and \( X = X_1 + X_2 + \ldots + X_m \) can be measured by the correlation between \( Y \) and \( X \), and this correlation can be used as the objective criterion to be searched for the \( \gamma_1 \), \( \gamma_2 \), \ldots , \( \gamma_m \) and \( w_1 \), \( w_2 \), \ldots , \( w_n \). This approach is a standard canonical correlation. In semilinar canonical correlation, the left-hand side of the equation, \( \gamma_1Y_1 + \gamma_2Y_2 + \ldots + \gamma_mY_m \), remains a linear combination of individual measures of the dependent variable and associated coefficients, but the right-hand side becomes a nonlinear function, in this case the bitemporal model relating effect-site concentration to drug effect. Semilinar canonical correlation estimates the coefficients \( \gamma_1 \), \( \gamma_2 \), \ldots , \( \gamma_m \) on the individual measures of the dependent variable, and it concurrently estimates the parameters of the nonlinear function. For mathematical tractability, we limited the number of bins (\( n \)) to 10. The measure of drug effect at time \( t \) the canonical univariate parameter for propofol at time \( t \), \( \text{CUP}_p(t) \), is thus the linear combination of the coefficients \( \gamma_1 \), \( \gamma_2 \), \ldots , \( \gamma_m \) with the measure of drug effect at time \( t \), \( Y_1(t) \), \ldots , \( Y_m(t) \).

\[
\text{CUP}_p(t) = \gamma_1Y_1(t) + \gamma_2Y_2(t) + \gamma_mY_m(t)
\]

where \( n \) = maximum number of bins (10 in the present case); \( Y_i \) = log (power from 0.5 to 5 Hz)/k; \( \gamma_i \) = log (power from 27.5 to 30 Hz)/k; \( \gamma_m \) is the first coefficient, and \( \gamma_n \) is the coefficient for the tenth bin. Our approach was to pool the data for all 48 study sessions. Let \( P_i(t) \) denote the powers in the 10 frequency bands measured at time \( t \) for the \( i \)-th volunteer, and let

\[
E^{(i)}(t) = \gamma_1 \log P_1(t) + \ldots + \gamma_m \log P_m(t)
\]

\( \gamma_1, \ldots , \gamma_m \) apply to all participants. Let

\[
E^{(i)}(t) = \frac{E_{\text{min}}^{(i)} + (E_{\text{max}}^{(i)} - E_{\text{min}}^{(i)})}{2} \cdot \frac{C_p(t)}{C_p(t)^{\beta_{\text{min}}} + C_p(t)^{\beta_{\text{max}}}}
\]

where \( C_p(t) = E_C(t)^{(i)} \)

be the biphasic pharmacodynamic model combining two \( E_C \) models. Observe that the \( i \)-th volunteer has his or her own values of the parameters \( E_{\text{min}}^{(i)} \), \( E_{\text{max}}^{(i)} \), \( \beta_{\text{min}}^{(i)} \), \( \beta_{\text{max}}^{(i)} \), and \( K_{\text{el}}^{(i)} \) (which determines \( CE^{(i)} \)).

The coefficients \( \gamma_1, \ldots , \gamma_m \) are not known for propofol. With semilinar canonical correlation, we calculate a single estimate of the coefficients. Our pooled approach is to estimate \( \gamma_1, \ldots , \gamma_m \), the individual parameters of the pharmacodynamic model and \( k_{el} \) for \( i = 1, \ldots , 48 \) by the values that minimize

\[
\sum_{i=1}^{48} \sum_{t=1}^{N-1} [E^{(i)}(t) - E^{(i)}(t)]^2
\]

subject to the constraint

\[
\frac{1}{N-1} \sum_{i=1}^{48} \sum_{t=1}^{N-1} [E^{(i)}(t) - E^{(i)}(t)]^2 = 1
\]

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where \( N \) is the total number of observations in the 48 study sessions and

\[
E = \frac{1}{N} \sum_{i=1}^{48} \sum_{t=1}^{E(t)}
\]

\( E(t) \) is the EEG effect at time \( t \), calculated for subject \( i \) using the population coefficients as the weights to the log power in the frequency bins.

The goodness of fit was assessed using the coefficient of determination, defined as

\[
R^2 = 1 - \frac{SSE}{SSTO}
\]

where

\[
SSTO = \sum (Y_i - \bar{Y})^2
\]

\[
SSE = \sum (Y_i - \bar{Y})^2
\]

where

\( \bar{Y}_i \) = the mean of the observed effect in a participant,

\( \bar{Y}'_i \) = the predicted effect of a participant, and

\( Y'_i \) = the observed effect in a participant.