Predictability of Processed Electroencephalography Effects on the Basis of Pharmacokinetic–Pharmacodynamic Modeling during Repeated Propofol Infusions in Patients with Extradural Analgesia

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Background: Pharmacokinetic–pharmacodynamic (PKPD) modeling can be used to characterize the concentration–effect relation of drugs. If the concentration–effect relation of a hypnotic drug is stable over time, an effect parameter derived from the processed electroencephalographic signal may be used to control the infusion for hypnosis. Therefore, the stability of the propofol concentration–electroencephalographic effect relation over time was investigated under non–steady state conditions.

Methods: Three propofol infusions (25 mg · kg$^{-1}$ · h$^{-1}$ for 10 min, 22 mg · kg$^{-1}$ · h$^{-1}$ for 10 min, and 12.5 mg · kg$^{-1}$ · h$^{-1}$ for 20 min) were administered to 10 patients during extradural analgesia. Each successive infusion was started immediately after the patient had regained responsiveness after termination of the preceding infusion. Electroencephalography was recorded from bilateral prefrontal to mastoid leads. Electroencephalographic amplitude in the 11- to 15-Hz band and the Bispectral Index were used as electroencephalographic effect variables. PKPD parameters were calculated with use of parametric and nonparametric models based on electroencephalographic data and arterial propofol concentrations derived during the initial infusion, and these were used to predict electroencephalographic effect during the subsequent infusions. The predictability of the electroencephalographic effects was determined by the coefficient of determination ($R^2$) and of the $-2 \log$ likelihood of the sequential infusions.

Results: The direction of electroencephalographic changes in response to the infusions was reproducible. Although PKPD parameters could be estimated well during the initial infusion (median [range] parametric $R^2 = 0.74$ [0.56–0.95] for electroencephalographic amplitude and 0.90 [0.27–0.99] for Bispectral Index), none of the modeling techniques could predict accurately the electroencephalographic effect during subsequent infusions ($R^2 = 0.00$ [−0.31–0.46] for electroencephalographic amplitude and 0.15 [−0.46–0.57] for Bispectral Index; $P < 0.01$).

Conclusions: The relation between blood propofol concentrations and the electroencephalographic effect under non–steady state conditions is not stable over time and is too complex to be modeled by any of the applied PKPD models.

PHARMACOKINETIC–pharmacodynamic (PKPD) modeling is used to characterize the concentration–effect relation of drugs and to compare drug potencies. Once individual PKPD parameters have been estimated, PKPD modeling may predict future drug effects,1 provided that the concentration–effect relation of a drug is stable over time. If this is the case, an effect parameter derived from the processed electroencephalographic signal could be used to control the propofol infusion rate in order to maintain hypnosis or sedation. However, the reproducibility of electroencephalographic effects during repetitive infusions has never been studied. In a previous study2 we modeled biphasic electroencephalographic effects in response to increasing and decreasing propofol concentrations during and after a single brief propofol infusion (10 min; 0.5 mg · kg$^{-1}$ · min$^{-1}$). In the present study we aimed to test the hypothesis that the concentration–electroencephalographic effect relation of propofol in patients is stable over time and that PKPD modeling can predict electroencephalographic effects during subsequent infusions, once individual PKPD parameters are derived from the initial infusion. Therefore, we investigated the reproducibility of two electroencephalographic effect variables in response to three successive propofol infusions as well as the adequacy of parametric and nonparametric PKPD modeling of the data acquired during and after the first infusion, as a predictor of the value of the electroencephalographic parameters during and after the second and third infusions. We also related the values of the electroencephalographic parameters to the times of loss and regaining of consciousness during and after the three infusions to test the stability of the relation between the electroencephalographic effect variable and these clinical parameters. As electroencephalographic effect variables, we studied the amplitude in the 11- to 15-Hz band, determined with aperiodic analysis, and the Bispectral Index (BIS) value, derived from bispectral analysis.

Patients and Methods

The study was approved by the Medical Ethical Committee of the University Hospital of Groningen, Groningen, The Netherlands. After obtaining written informed consent, we studied 10 patients (5 men; American Society of Anesthesiologists physical status, I or II; age [median and range], 58 [22–75] yr; weight, 81 [60–90] kg; height, 1.71 [1.57–1.80 m]) who were scheduled for elective major knee surgery that would...
last approximately 2 h. Patients with a history of recent intake of drugs that might affect the electroencephalogram, an alcohol intake in excess of 30 g/d, neurologic disorders, or extreme nervousness were excluded. No oral intake was allowed after midnight before the operation. No premedication was administered.

Before surgery, an intravenous cannula was inserted and 0.9% saline, 500 ml, was infused rapidly as fluid loading. Extradural analgesia was achieved by the administration of a single bolus dose of 0.5% bupivacaine through an epidural catheter inserted at the L3–L4 level, 5 min after administration of a test dose of 3 ml bupivacaine 0.5% with 15 μg adrenaline. The dose was adjusted to achieve a sensory block for cold to at least T10. Forty minutes after the epidural administration of bupivacaine, an infusion of propofol, 25 mg · kg\(^{-1}\) · h\(^{-1}\), was started and continued for 10 min. Surgery was started after the patient lost responsiveness to verbal commands. When the patient regained responsiveness after termination of the infusion, a second infusion of propofol was started at a rate of 22 mg · kg\(^{-1}\) · h\(^{-1}\) for 10 min. When the patient regained responsiveness again, a third infusion of propofol at a rate of 12.5 mg · kg\(^{-1}\) · h\(^{-1}\) was given for 20 min.

Three-lead echocardiographic readings, automatic noninvasive blood pressure, oxygen saturation measured by pulse oximetry (SpO\(_2\)) and end-tidal carbon dioxide concentrations were monitored continuously. If ventilation became insufficient during the infusion of propofol, as indicated by an SpO\(_2\) below 92%, an obstructed airway, or an end-tidal carbon dioxide concentration of more than 6%, ventilation was assisted manually with a face mask and oxygen-enriched air (40% O\(_2\)). When the systolic blood pressure decreased by more than 25% below the baseline value (calculated as the average of the blood pressures measured at hospital admission, on the morning of surgery, and on arrival at the anesthesia room), phenylephrine, 0.1 mg intravenously, was administered every minute until correction of blood pressure to more than 25% below baseline value. When the heart rate decreased below 50 beats/min, methylatropine, 0.25 mg intravenously, was administered.

Responsiveness was determined by testing the response of the patient to simple commands from a pre-recorded tape (to raise the thumb, to spread the fingers, or to clench the fist), given through headphones every 60 seconds. The time at which the patient no longer responded to verbal commands was noted as loss of responsiveness, and the time at which the patient started to respond to verbal commands was marked as regaining of responsiveness.

**Electroencephalographic Recording and Analysis**

The electroencephalographic readings were recorded from bilateral mastoid to prefrontal leads (M\(_1\)–F\(_P1\), M\(_2\)–F\(_P2\), with F\(_Pz\) as reference), with use of Ag/AgCl electroencephalographic electrodes fixed to the skin with adhesive tape. Electrode impedance was maintained below 5 kΩ. A 5-min baseline electroencephalogram was recorded before the institution of epidural analgesia with the patient supine and with the eyes closed. After the onset of epidural analgesia, the electroencephalogram was recorded continuously from 5 min before the start of the propofol infusion until the patient regained consciousness after the last infusion. For electroencephalographic recording, the amplifiers of the Lifescan EEG monitor (Diatek, San Diego, CA) were used. The raw electroencephalographic signal was stored on FM tape for off-line analysis. Data recorded from the nondominant hemisphere (based on the handedness of the patient) were used for analysis.

For electroencephalographic analysis, we used aperiodic analysis\(^3\) and bispectral analysis\(^4\). For aperiodic analysis we used the Lifescan EEG monitor, software version 4.3 (Diatek), to calculate amplitudes in the 11- to 15-Hz frequency band. Data were averaged over periods of 30 s. Periods containing electromyographic artifacts, as indicated by an amplitude of more than 15 μV/s in the frequency band 26–30 Hz, were excluded from analysis. Aperiodic analysis thus calculates electroencephalographic data from the preceding 30 s. The time lag that is introduced by the epoch duration over which the electroencephalographic variable is calculated might influence determination of PKPD parameters. To minimize this effect, we used the midpoint of the 30-s epoch (= 15 s) as the time related to the electroencephalographic amplitude value.

For bispectral analysis, the electroencephalographic signal was analyzed with the Aspect A-1000 (Aspect Medical Systems, Natick, MA; BIS version 3.12) to calculate the BIS value. The high-pass filter was set at 2 Hz and the low-pass filter at 30 Hz. The 50-Hz filter was activated. BIS was smoothed over a 15-s interval. Data containing artifacts, as indicated by the built-in artifact detection, were rejected. BIS values are calculated over the preceding 45 s as the result of the internal 30-s smoothing of the BIS version 3.12 and the additional 15-s smoothing. During smoothing, all BIS data are weighted equally. Therefore, we used the midpoint of the 45-s epoch as the time related to the calculated BIS value.

The time course of the electroencephalographic parameters was studied and related to blood propofol concentrations, to the times at which the patient became unresponsive to verbal command, and to the times at which responsiveness regained.

**Propofol Kinetics and Dynamics**

A 20-gauge cannula was inserted in a radial artery for sampling of arterial blood for propofol concentration estimation. Blood samples of 3 ml were taken just before
the start of each consecutive propofol infusion and sequentially every 2 min. During the low-speed infusion, samples were taken every 4 min. Thirty minutes after the start of the third infusion, the sampling rate was decreased, and samples were taken at 33, 36, 40, 55, 70, 100, and 130 min after the start of the third infusion (total volume of blood samples, 130 ml). The blood was mixed with EDTA and stored at 4°C until determination of whole blood propofol concentrations with high-performance liquid chromatography, according to the method of Plummer et al.5 (detection limit, 5 μg/l; coefficient of variation, 4.3%). At all electroencephalographic data points, blood concentrations were calculated with use of linear interpolation between measured concentrations during increases in blood concentrations, as well as logarithmically between the measured concentrations during decreases in concentrations.

For PKPD modeling of the electroencephalographic effects of propofol, we applied one nonparametric and two different parametric models. In all models the concentration in the brain (the effect compartment) was assumed to be linearly linked to the arterial blood concentration.6 The concentration in the effect compartment (the brain) was estimated with use of the formula

\[
\frac{dC_e}{dt} = keo(C_b - C_e)
\]

where \(C_e\) is the concentration in the hypothetical effect compartment, \(C_b\) is the blood concentration, and \(keo\) is a first-order rate constant, describing the rate of equilibration between the blood and the effect site.

The nonparametric model was used to model both the aperiodic analysis and the bispectral analysis data. This model is descriptive, and no mathematical relation between the concentration in the brain and the electroencephalographic effect is presumed. \(Keo\) was estimated by minimizing the area of the hysteresis loop of the electroencephalographic effect versus effect compartment concentration.7,8 After minimization of the concentration–effect hysteresis loop, remaining differences in effect for a particular concentration were averaged to acquire a unique effect compartment–concentration–effect relation. This concentration–effect relation was used to predict electroencephalographic effect during subsequent infusions on the basis of effect compartment concentrations calculated from the estimated \(keo\) and the measured blood concentrations.

The parametric model used to fit the bispectral analysis data was the sigmoid \(F_{max}\) model, in which the formula is

\[
E = \left( E_0 + \frac{F_{max} \cdot C_e^\gamma}{EC_{50} + C_e} \right)
\]

where \(E_0\) is the baseline effect, \(F_{max}\) is the maximal achievable effect, \(C_e\) is the concentration in the effect compartment, \(EC_{50}\) is the concentration at which 50% of the maximal achievable effect is obtained, and \(\gamma\) is the exponent that determines the slope of the concentration–response curve.

The parametric model we used to fit the data derived with aperiodic analysis was the biphasic parametric modeling technique of Mandema and Danhof.9 This model assumes that the measured electroencephalographic effect of propofol is the resultant of its effect in two different effect compartments with different equilibration constants, \(keo1\) and \(keo2\). Increasing propofol concentrations in these two effect compartments have opposing effects on the electroencephalographic amplitude, i.e., activation and inhibition. The formula of the relation between effect (E) and concentration is

\[
E = \left( E_0 + \frac{F_{max1} \cdot C_{1}^{\gamma1}}{EC_{501} + C_{1}} \right) \cdot \left( 1 - \frac{C_{2}^{\gamma2}}{EC_{502} + C_{2}} \right)
\]

where \(E_0\) is the baseline effect, \(F_{max}\) is the hypothetical maximal increase of electroencephalographic amplitude when no electroencephalographic inhibition would occur, \(EC_{50}\) is the steady state concentration at which half of \(F_{max}\) occurs, \(C_1\) is the concentration in effect compartment 1, \(C_2\) is the concentration in effect compartment 2, and \(\gamma\) determines the slope of the curves. The parametric model parameters, including \(keo\) values, were estimated by minimizing the sum of squares between observed and predicted effect values. The range of values of \(keo1\) and \(keo2\) was restricted to 0.05–10/min; of \(\gamma\), to 0.5–10; and of \(EC_{50}\) to 1–10 mg/l, to prevent nonphysiologic outcomes. For calculations, the Solver tool from Microsoft Excel 7 (Microsoft, Redmond, WA) was used. Precision of the derived pharmacodynamic parameters was determined by calculations of the standard error of determination.10

Individual pharmacodynamic parameters for each model were calculated on the basis of data acquired during the first infusion. The electroencephalographic effects of the second and the third infusion were predicted on the basis of all measured and interpolated propofol concentrations with use of these calculated parameters.

The quality of fit was expressed as the coefficient of determination, \(R^2\):

\[
R^2 = 1 - \frac{\sum (E_{observed} - E_{modeled})^2}{\sum (E_{observed} - E_{average})^2}
\]

where \(E_{average}\) is the average of the observed effect values.

The bias of prediction was expressed as the median performance error (MDPE).

\[
PE = \frac{E_{observed} - E_{modeled}}{E_{modeled}} \times 100\%
\]
The $R^2$ and MDPE of the initial and the combined subsequent infusions were compared both for individual patients and between the modeling techniques.

Adequacy of the PKPD parameters derived from the initial infusion to predict the electroencephalographic effect of the subsequent infusions was determined by comparison of the $-2 \log$ likelihood of the electroencephalographic effects of the combined second and third infusion, when calculated with the derived PKPD parameters from the initial infusion or with the optimal PKPD parameters for the combined second and third infusions. Optimal PKPD parameters for the combined second and third infusions were determined from electroencephalographic data obtained during and after the second and third infusions, and the blood propofol concentrations of all three infusions were determined by minimizing the sum of squares between observed and fitted electroencephalographic effect:

$$-2 \log \text{likelihood} = n \ln \left( \sum_{i=1}^{n} (E_{\text{observed}} - E_{\text{modeled}})^2 \right) + n - n \ln n - n \ln \pi$$

where $n$ is the number of observed electroencephalographic values.

The measured electroencephalographic amplitudes and BIS values at the times of loss and regaining of responsiveness during the three infusions were compared. In addition, for aperiodic analysis, the measured times of occurrence of the electroencephalographic maxima during all three infusions were compared to the times predicted by the models and to the times of loss and regaining of responsiveness.

Statistical Analysis

Comparisons were made with use of the Friedman nonparametric test for repeated measures ANOVA for related samples. When indicated, Wilcoxon signed rank tests were used for subsequent comparisons. For comparison of the $-2 \log$ likelihood of the predicted versus optimal PKPD values of the sequential infusions, chi-square statistics were applied. The degree of freedom was the number of nonfixed PKPD parameters. $P < 0.05$ was considered significant. The computer program SPSS for Windows (version 6.1.3; SPSS, Chicago, IL) was used for statistical calculations. Data are expressed as medians and ranges.

Results

Extradural analgesia was adequate in all patients (sensory level to cold, T8 [T2–T10]). Seven patients required administration of phenylephrine intravenously to correct hypotension: four during the initial infusion, five during the fast infusion, and five during the slow infusion. Four patients required administration of methylatropine intravenously to correct bradycardia. All patients required ventilatory support during the periods of unresponsiveness.

In one patient, adequate electrode impedance could not be maintained, which resulted in unacceptable artifacts. We had to administer ephedrine to another patient because the blood pressure could not be corrected with phenylephrine. However, because ephedrine may cause arousal and, as a result, electroencephalographic changes, this patient was excluded from further analysis. For a third patient the surgery was terminated before the third infusion was started, so no data could be obtained for the third infusion. One patient’s electroencephalographic data from the fast infusion were lost after processing for aperiodic analysis. Seven patients could therefore be

![Figure 1: Box plots of the electroencephalographic (EEG) amplitude and the Bispectral Index (BIS) values observed at loss of responsiveness during the first (L1), fast (Lf), and slow (Ls) infusions, at the regaining of responsiveness after termination of the first (R1), fast (Rf), and slow (Rs) infusions, and at baseline (Base), minimal value (Min), and maximal value (Max). The boxes represent median, 25th–75th percentiles, and range, including extremes (□).](http://anesthesiology.pubs.asahq.org/pdfaccess.ashx?url=/data/journals/jasa/931224/ on 11/13/2018)
evaluated completely, and one patient was evaluated for only two infusions. For one patient, BIS data were not available from the fast infusion.

Aperiodic analysis
With use of aperiodic analysis, the electroencephalographic amplitude in the 11- to 15-Hz band showed a biphasic response to increasing blood propofol concentrations, e.g., there was an initial increase in electroencephalographic amplitude, from a baseline value of 33 μV/s (16–95) to a maximum of 193 μV/s (147–484), followed by a decrease to 13 μV/s (0–26). When blood propofol concentrations decreased after termination of the infusion, electroencephalographic amplitude again showed a biphasic effect. During the second and third infusions, similar electroencephalographic amplitude sequences were observed. The electroencephalographic amplitudes at loss of and regaining of responsiveness are shown in figure 1.

The sequence of events was identical during and after each of the three infusions, i.e., the patients lost responsiveness just before or during the first electroencephalographic amplitude maximum and regained responsiveness after the electroencephalographic amplitude maximum that occurred following termination of each infusion (table 1; $P < 0.03$). $K_{\text{eo}}$ was 0.34/min (0.16–0.45) for the nonparametric model. PKPD parameters for the parametric model are displayed in table 2. The times of occurrence the electroencephalographic amplitude maxima could be predicted well on the basis of PKPD modeling of the initial infusion. Electroencephalographic amplitude during the subsequent infusions was predicted poorly on the basis of PKPD parameters derived from the initial infusion (table 2, figs. 2 and 3). No bias was observed in the prediction of the electroencephalographic effect with the use of parametric and nonparametric modeling techniques.

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Table 1. Time of Events Related to the Start of Each Infusion

<table>
<thead>
<tr>
<th>Infusion 1</th>
<th>LOR (min)</th>
<th>Maximum 1 (min)</th>
<th>Maximum 2 (min)</th>
<th>ROR (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial infusion, 25 mg · kg$^{-1}$ · h$^{-1}$ (10 min)</td>
<td>3.5 (2–6)</td>
<td>4 (2–7)</td>
<td>17 (14–21)</td>
<td>25 (16–40)</td>
</tr>
<tr>
<td>Fast infusion, 22 mg · kg$^{-1}$ · h$^{-1}$ (10 min)</td>
<td>3 (0–5)</td>
<td>4 (2–7)</td>
<td>28 (23–32)</td>
<td>32 (29–40)</td>
</tr>
<tr>
<td>Slow infusion, 12.5 mg · kg$^{-1}$ · h$^{-1}$ (20 min)</td>
<td>2 (0–4)</td>
<td>3 (2–4)</td>
<td>19 (14–26)</td>
<td>29 (19–47)</td>
</tr>
</tbody>
</table>

Values are expressed as median (range).

LOR = loss of responsiveness; maximum 1 = electroencephalographic amplitude maximum during increasing propofol concentration; maximum 2 = electroencephalographic amplitude maximum during decreasing propofol concentration; ROR = regaining of responsiveness.

Table 2. Parametrically Estimated PKPD Parameters ± Standard Error

<table>
<thead>
<tr>
<th>Patient</th>
<th>$k_{\text{eq1}}$ (min$^{-1}$)</th>
<th>$k_{\text{eq2}}$ (min$^{-1}$)</th>
<th>$EC_{25}$ (mg/l)</th>
<th>$\gamma$</th>
<th>$\delta$ – 2LL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amplitude</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.32 ± 0.03</td>
<td>0.24 ± 0.03</td>
<td>5.1 ± 0.3</td>
<td>2.4 ± 0.2</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>0.26 ± 0.05</td>
<td>0.43 ± 0.09</td>
<td>3.7 ± 0.3</td>
<td>2.9 ± 0.5</td>
<td>2.76</td>
</tr>
<tr>
<td>4</td>
<td>0.22 ± 0.07</td>
<td>0.20 ± 0.06</td>
<td>3.3 ± 0.6</td>
<td>2.5 ± 0.6</td>
<td>0.20</td>
</tr>
<tr>
<td>5</td>
<td>0.24 ± 0.02</td>
<td>0.24 ± 0.02</td>
<td>3.6 ± 0.1</td>
<td>2.4 ± 0.2</td>
<td>0.48</td>
</tr>
<tr>
<td>6</td>
<td>0.63 ± 0.12</td>
<td>0.26 ± 0.03</td>
<td>2.6 ± 0.3</td>
<td>2.5 ± 0.2</td>
<td>1.00</td>
</tr>
<tr>
<td>7</td>
<td>0.21 ± 0.01</td>
<td>0.17 ± 0.01</td>
<td>3.2 ± 0.1</td>
<td>5.0 ± 0.4</td>
<td>0.24</td>
</tr>
<tr>
<td>9</td>
<td>0.29 ± 0.01</td>
<td>0.36 ± 0.01</td>
<td>4.8 ± 0.1</td>
<td>4.5 ± 0.2</td>
<td>0.21</td>
</tr>
<tr>
<td>10</td>
<td>0.32 ± 0.02</td>
<td>0.31 ± 0.02</td>
<td>3.7 ± 0.1</td>
<td>3.4 ± 0.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Median</td>
<td>0.27</td>
<td>0.25</td>
<td>3.6</td>
<td>2.7</td>
<td>0.28</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.21 ± 0.01</td>
<td></td>
<td>1.7 ± 0.1</td>
<td>2.7 ± 0.3</td>
<td>0.62</td>
</tr>
<tr>
<td>2</td>
<td>0.22 ± 0.00</td>
<td></td>
<td>2.6 ± 0.0</td>
<td>4.3 ± 0.2</td>
<td>0.76</td>
</tr>
<tr>
<td>4</td>
<td>0.15 ± 0.00</td>
<td></td>
<td>2.6 ± 0.0</td>
<td>5.9 ± 0.6</td>
<td>0.46</td>
</tr>
<tr>
<td>5</td>
<td>0.08 ± 0.00</td>
<td></td>
<td>2.7 ± 0.1</td>
<td>5.4 ± 0.8</td>
<td>0.67</td>
</tr>
<tr>
<td>6</td>
<td>0.36 ± 0.02</td>
<td></td>
<td>1.2 ± 0.0</td>
<td>10.0 ± 3.3</td>
<td>0.45</td>
</tr>
<tr>
<td>7</td>
<td>0.07 ± 0.02</td>
<td></td>
<td>1.0 ± 2.4</td>
<td>0.5 ± 0.4</td>
<td>0.65</td>
</tr>
<tr>
<td>9</td>
<td>0.20 ± 0.01</td>
<td></td>
<td>5.4 ± 1.8</td>
<td>1.0 ± 0.1</td>
<td>0.65</td>
</tr>
<tr>
<td>10</td>
<td>0.14 ± 0.01</td>
<td></td>
<td>2.3 ± 0.1</td>
<td>3.8 ± 0.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Median</td>
<td>0.18</td>
<td></td>
<td>2.4</td>
<td>4.0</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Parameters are for amplitude and Bispectral Index (BIS) during the initial infusion and the combined sequential infusions and the resulting difference in –2 log likelihood ($\delta$ – 2LL) of the fit of the combined sequential infusions when calculated with these fixed pharmacokinetic–pharmacodynamic (PKPD) parameters or calculated with the optimal PKPD parameters.

* $P < 0.001$.

$k_{\text{eq1}}$ = first effect-site equilibration constant; $k_{\text{eq2}}$ = second effect-site equilibration constant; $EC_{25}$ = effect-site concentration at 50% of maximum achievable effect; $\gamma$ = slope of concentration–response curve.
Bispectral Analysis

Using the BIS analysis, we observed a rapid decrease of the BIS value from a baseline of 98 (96–98), followed by a much slower decrease during increasing blood concentrations, to a minimum value of 40 (22–57). When blood concentrations decrease, BIS values first increase slowly and then rapidly because of (or simultaneously with) awakening. In two patients, after loss of responsiveness, we observed an unexplained increase in the BIS value during increasing blood concentrations. BIS values at loss and regaining of consciousness are shown in figure 1.

Keo estimated with nonparametric modeling of BIS data was 0.17 min (0.08–0.24) \( (P = 0.017 \) for comparison with aperiodic analysis). Pharmacodynamic parameters and their standard errors estimated with parametric modeling are presented in table 2. In one patient the EC\text{50} reached the lower constraint. The BIS-derived models were also unable to predict BIS values during subsequent infusions on the basis of PKPD parameters derived from the initial infusion (table 2, figs. 2 and 3). No bias was observed in the prediction of the electroencephalographic effect with use of either modeling technique.

Discussion

In the present study we assessed the reproducibility of propofol electroencephalographic effects during successive infusions and found that both parametric and nonparametric PKPD models derived from the first infusion were unable to predict the pharmacodynamic relation during the subsequent infusions. Other investigators have administered repeated infusions but did not model the concentration–effect relation and either studied the correlation between electroencephalographic effect and clinical responses or used closed-loop strategies.\textsuperscript{11,12}

We applied a dosing regimen in which the initial infusion of propofol (25 mg·kg\textsuperscript{-1}·h\textsuperscript{-1}) would induce pronounced electroencephalographic changes to allow determination of the concentration–response relation. The second fast infusion was at a slightly slower rate

\[ R^2 \]  

\[ \text{Median Performance Error} \]

\[ \text{Amplitude 11-15 Hz} \]

\[ \text{BIS} \]

\[ \text{Blood concentration} \]

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(22 mg · kg\(^{-1} \cdot \text{h}^{-1}\)), with the aim of mimicking the rate of changes of the initial infusion but preventing higher concentrations caused by residual drug from the initial infusion. Nonparametric modeling would not have allowed prediction of electroencephalographic effect for such higher concentrations. With the slow infusion (12.5 mg · kg\(^{-1} \cdot \text{h}^{-1}\)), we administered the same drug dose at a slower rate, as administered at the initial infusion, with the aim of slowing the concentration changes. With this dosing regimen we intended to investigate PKPD modeling under different non–steady state conditions.

In this study we confirm that the propofol concentration–electroencephalographic amplitude relation is consistently biphasic. In the previous study,\(^2\) in which propofol was administered in a single infusion, the propofol concentration–electroencephalographic effect relation was modeled successfully with the “Mandema model.”

Parametric as well as nonparametric modeling predicted reasonably well the times of occurrence of the electroencephalographic amplitude maxima during the subsequent infusions. However, neither parametric nor nonparametric modeling of the initial infusion for electroencephalographic amplitude and BIS effect allowed adequate prediction of the electroencephalographic effect during subsequent infusions.

The negative values of some \(R^2\) values obtained for the prediction of the electroencephalographic effects of subsequent infusions seem strange. If the pharmacodynamic variables were free to be optimized, as under modeling conditions, the worst possible outcome would have been a straight line through the average observed value (\(R^2 = 0\)), which represents no concentration–effect relation. However, the pharmacodynamic variables for the subsequent infusions were derived from the initial infusion and were fixed during the subsequent infusions. Therefore, \(R^2\) could become less than zero.

Reasons for the poor prediction of electroencephalographic effect during subsequent infusions might include the choice of patients scheduled for a surgical intervention, the epoch length over which the electroencephalographic effect variable is calculated, the pharmacodynamic model applied, the cerebral blood flow changes in response to the drug administered, the occurrence of acute tolerance, interaction with a time-related change in the extradural block level, or lack of stimuli to the patient. Because many patients are nervous before the operation, the electroencephalographic changes during the initial infusion and the transition from a state of full consciousness and alertness to unconsciousness will be more pronounced than during subsequent infusions, in which patients start from a state of responsiveness but are still sedated. Modeling of the electroencephalographic effects of the first infusion might then overestimate electroencephalographic changes, resulting in less accurate estimation of PKPD parameters. Moreover, during full consciousness, more EMG artifacts may be present, possibly resulting in higher-frequency components contaminating the derived electroencephalographic parameters.

The epoch length over which the electroencephalographic effect variables are calculated introduces a time delay between the concentration in the brain and the observed effect. This delay might have reduced the accuracy of estimation of the equilibration constant(s). To minimize inaccuracy in determination of the equilibration constant \(k_{eq}\), we applied a time correction for the epoch duration. Such a correction has the disadvantage that electroencephalographic data that lay ahead of the linked time point are used for calculation and prediction. In a clinical setting, only real-time data are available, and as a result it is difficult to construct an algorithm that incorporates such a time correction to predict electroencephalographic effect. Initially we studied the predictability of the electroencephalographic data on the basis of PKPD modeling of the real-time acquired electroencephalographic data. That analysis could not predict subsequent electroencephalographic effect, which necessitated the application of the presented time correction for the time lag caused by the epoch duration. Apart from a time shift, a long epoch length introduces an averaging of effect, which causes inaccuracy when the electroencephalogram changes rapidly.

The “Mandema model” we applied for modeling the electroencephalographic amplitude has been applied successfully to model the biphasic electroencephalographic amplitude effects of a single propofol infusion\(^2\) and has the potential to deal with unequal electroencephalographic effect during onset and offset. However, this published model has not been validated yet, and there is a possibility that this model might play a role in the poor prediction of the subsequent infusions. The Sheiner model we applied for modeling the BIS effect of propofol is a widely accepted model of the PKPD effects of several anesthetic drugs such as opioids,\(^13\) midazolam,\(^14\) and neuromuscular blocking agents.\(^5\)\(^,\)\(^15\) However, with this model it was not possible to predict BIS effects of propofol of the subsequent infusions. Parametric models have a disadvantage in that assumptions are made about the shape of the concentration–effect relation. These assumptions may be unjustified and may be the cause of the poor prediction. Therefore, we also modeled the concentration–effect relation nonparametrically. Such modeling makes no assumptions about the shape of the concentration–effect relation. This model assumes only a single effect compartment that is linearly linked to the central compartment; therefore, it should predict the subsequent electroencephalographic effects best. However, it did not predict electroencephalographic amplitude and BIS effects during subsequent infusions better than parametric modeling.
Propofol may influence local cerebral blood flow and consequently its distribution. Ludbrook et al.\textsuperscript{16} demonstrated that propofol decreases local cerebral blood flow in sheep in a concentration-dependent manner. When cerebral flow decreases more than the flow to the radial artery during increasing concentrations, the equilibration constant, $k_{eq}$, which describes the time lag between the measured radial artery blood propofol concentration and the concentration in the brain, will decrease.\textsuperscript{17} These changes in cerebral blood flow would have been most prominent during the first infusion, as the concentration changes were largest at that time.

Both acute tolerance\textsuperscript{18} and a decreased sensitivity for the hypnotic effect of propofol, resulting from a decreasing intensity of extradural block over time,\textsuperscript{19} could account for the discrepancies between predicted and observed electroencephalographic effect during the subsequent infusions. To detect a possible decreased electroencephalographic effect of propofol concentrations, we estimated EC\textsubscript{50} values for the two sequential infusions and compared these to the EC\textsubscript{50} values derived from the initial infusions. EC\textsubscript{50} values derived from the initial and the sequential infusions were not different, and we observed no significant bias during the subsequent infusions. Therefore, these two factors are unlikely to contribute significantly to the observed discrepancies in electroencephalographic effects.

When pharmacologically induced unconsciousness turns into natural sleep, the relation between the electroencephalogram and the drug concentration might become obscured. Such a transition was suggested by Schwilden et al.\textsuperscript{20} as an explanation for the absence of electroencephalographic response to decreasing drug concentrations in volunteers who were not stimulated during closed-loop studies with methohexitan. When the investigators administered random stimuli, electroencephalographic changes were sufficient to adjust the methohexitan infusion rate to prevent awareness. We cannot exclude that natural sleep occurred in one of our patients. However, we believe that patients during major knee surgery undergo sufficient randomly administered stimuli such as movement from surgery, operating theater noises, and manipulation, for maintenance of ventilation that is adequate for prevention of natural sleep. Unlike Schwilden et al.,\textsuperscript{20} we did not observe periods during which electroencephalographic variables did not change in response to changing drug concentrations.

Probably the most important reason for the discrepancies between observed and predicted electroencephalographic effects is that the electroencephalographic signal is the net electrical effect of a very complex system of electrical activity of many nerve fibers in several brain areas, with many interactions measured from the skull. Because of this complexity, the electroencephalographic signal is not necessarily a simple function of the blood concentration of the drug. This relation is likely to become even more obscured when blood concentrations are changing and each subsystem or any particular cortical area responds in its own way. The observation that the electroencephalographic amplitude or BIS effect of subsequent infusions cannot be predicted accurately means that there is no consistent relation between blood propofol concentrations and electroencephalographic effect during non-steady state situations. This finding does not preclude a consistent relation between the electroencephalographic effect variables and the level of sedation or hypnosis. Although the observation of similar electroencephalographic values at the loss and regaining of consciousness during the three infusions suggests a consistent relation between electroencephalographic effect variables and the level of sedation, this finding has limited power, as the time between the verbal commands limits the accuracy of determination of the moment of loss of responsiveness to 1 min.

In summary, we conclude that pharmacodynamic modeling of the electroencephalographic amplitude and the BIS effect during a propofol infusion with non-steady state blood concentrations provides insufficiently reliable data to predict electroencephalographic effect during subsequent infusions within the context of these models. PKPD modeling of electroencephalographic amplitude or BIS value in which the brain is considered an effect compartment linearly linked to the arterial blood concentration appears to be an oversimplification of the complex processes that occur in the central nervous system in response to propofol administration.

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References


