Quantitative electroencephalographic analysis of the biphasic concentration–effect relationship of propofol in surgical patients during extradural analgesia

K. KUIZENGA, C. J. KALKMAN, P. J. HENNIS

Summary
We studied effects on the EEG of propofol infused at a rate of 0.5 mg kg\(^{-1}\) min\(^{-1}\) for 10 min in 10 healthy male surgical patients under extradural analgesia. The EEG amplitude in six frequency bands was related to arterial blood propofol concentrations and responsiveness to verbal commands. The EEG amplitude showed a characteristic biphasic response to increasing blood propofol concentrations in all frequency bands. During the infusion, patients lost responsiveness when EEG amplitudes in the high frequency bands were decreasing after having reached a maximum. EEG changes were different during infusion and emergence. Pharmacodynamic modelling, using two effect compartments with dissimilar equilibration constants, resulted in satisfactory fits. We conclude that propofol exerts a biphasic effect on the EEG amplitude in all frequency bands. The dissimilarity of EEG changes during infusion and during emergence suggests that two effect compartments with different equilibration constants exert opposing effects on the EEG. (Br. J. Anaesth. 1998; 80: 725–732)

Keywords: monitoring electroencephalography; pharmacodynamics; propofol; biphasic modelling

Sedative doses of propofol significantly increase amplitude and power in the beta region of the EEG.\(^1\) Hypnotic doses of propofol, however, cause slowing of the EEG, manifested by an increase in delta power, reduced alpha and beta activity, and a lowering of the median frequency and spectral edge.\(^3\) This biphasic pattern of the EEG amplitude in the beta band in response to an increasing blood propofol concentration has been described qualitatively,\(^4\) but has not been studied quantitatively.

The aims of the present study were, first, to quantify the biphasic relationship between propofol concentration and EEG effects during the transition from the awake state to hypnosis and during subsequent emergence and second, to fit a pharmacodynamic model to the observed changes. The study of EEG changes caused by hypnotics in anaesthetized surgical patients is hindered by the effects of concurrently administered sedative and analgesic drugs. As extradural analgesia with bupivacaine appears to have no significant effect on the EEG,\(^6\) the study was performed in surgical patients under extradural analgesia, who received a 10-min propofol infusion.

Patients and methods
The study was approved by the Medical Ethics Committee of the University Hospital of Groningen. After obtaining written informed consent, we studied 10 healthy male patients, of mean (SD) age 28.4 (7.7) yr, weight 81 (12) kg and height 1.82 (0.12) m, scheduled for elective lower-limb surgery under extradural analgesia. Patients with a history of recent drug intake, an alcohol intake in excess of 30 g day\(^{-1}\), neurological disturbances, or extreme nervousness were excluded. No oral intake was allowed after midnight preceding the operation. No premedication was administered.

Before operation, an i.v. cannula was inserted and 0.9% saline 500 ml infused as fluid loading. Extradural analgesia was achieved by giving 0.5% bupivacaine 20 ml through an extradural catheter inserted at L3–L4 5 min after a test dose of 0.5% bupivacaine 3 ml with epinephrine 15 mg. Forty min after the extradural administration of bupivacaine, i.v. administration of propofol 0.5 mg kg\(^{-1}\) min\(^{-1}\) was started with a constant-rate infusion for 10 min (total dose 5 mg kg\(^{-1}\)). Surgery was started after the patient lost responsiveness.

A 3-lead ECG, automatic noninvasive arterial pressure, oxygen saturation and end-tidal carbon dioxide concentration were monitored continuously. If ventilation became insufficient during the infusion of propofol, as indicated by \(S\text{P}_\text{O}_\text{2}\) 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% \(O\text{}_2\)).

Responsiveness was determined by testing the response of the patient to simple commands from a prerecorded tape (“raise your thumb”, “spread your fingers”, and “clench your fist”), given via headphones every 30 s. It was noted when the patient became unresponsive, and when responsiveness returned after stopping the propofol infusion.
and related to the blood propofol concentrations, the time at which the patient became unresponsive to verbal command, and the time at which responsiveness was regained.

PROPOFOL KINETICS AND DYNAMICS

A 20 gauge cannula was inserted in a femoral artery for sampling of arterial blood after the onset of extradural analgesia. This sample site was chosen to minimize patient discomfort. Blood samples of 3 ml were taken at 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 25, 30, 40, 55, 70, 100, 130, and 190 min after the start of the propofol infusion and mixed with EDTA. Blood samples were stored at 4°C until determination of whole-blood propofol concentrations with high performance liquid chromatography (detection limit 5 µg l⁻¹, coefficient of variation 4.3%).

Bi- and tri-exponential functions were fitted to concentration vs time data using weighted (log concentration) least-squares nonlinear regression analysis (software package Multifit, J. H. Proost, University of Groningen, The Netherlands). A bi- or tri-exponential function was chosen on the basis of the Schwartz criterion. The following pharmacokinetic parameters were derived using standard equations: volume of the central compartment (Vc), volume of distribution at steady state (Vss), plasma clearance (CL), distribution (T1/2γ), T1/2α, and elimination (T1/2β) half-lives. Fitted data of individual patients were used to calculate the time course of the blood propofol concentration in each patient, to estimate the propofol concentrations at the time of loss and return of responsiveness, and at the time of the EEG amplitude maxima.

Figure 1 Measured blood propofol concentrations during the first 35 min after the start of the propofol infusion. Infusion rate 0.5 mg kg⁻¹ min⁻¹. Duration 10 min (total dose 5 mg kg⁻¹). Linear interpolation between measured data points was applied to draw lines.

Figure 1

Table 1 Pharmacokinetic values expressed as mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>Three compartments (n = 7)</th>
<th>Two compartments (n = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t1/2α (min⁻¹)</td>
<td>1.00 (0.52)</td>
<td>1.33 (0.31)</td>
</tr>
<tr>
<td>t1/2α (min⁻¹)</td>
<td>9.54 (4.34)</td>
<td></td>
</tr>
<tr>
<td>t1/2γ (min⁻¹)</td>
<td>74.4 (19.1)</td>
<td>55.2 (12.4)</td>
</tr>
<tr>
<td>Vc (l kg⁻¹)</td>
<td>0.10 (0.04)</td>
<td>0.09 (0.09)</td>
</tr>
<tr>
<td>Vss (l kg⁻¹)</td>
<td>1.31 (0.30)</td>
<td>1.45 (0.83)</td>
</tr>
<tr>
<td>CL (ml kg⁻¹ min⁻¹)</td>
<td>28.2 (5.39)</td>
<td>32.5 (6.11)</td>
</tr>
</tbody>
</table>
Biphasic propofol concentration effect on the ECG

interpolation between measured $C_p$ values during infusion and log–linear interpolation between the measured $C_p$ values after the infusion. In the present study we allowed one or two values for $k_e$ during fitting. When only one $k_e$ is allowed the concentrations in C2 and C1 are identical and the model could be considered to consist of one effect compartment. The quality of fit was expressed as the coefficient of determination, $R^2$.

$$R^2 = 1 - \frac{\sum (E_{\text{observed}} - E_{\text{modelled}})^2}{\sum (E_{\text{modelled}} - E_{\text{mean}})^2}$$

STATISTICAL ANALYSIS

As it could not be ascertained if the EEG amplitude data derived from aperiodic analysis in 10 patients were normally distributed, EEG data are presented as medians and 25–75 percentiles. Pharmacokinetic data are expressed as mean (SD). Pharmacodynamic data are expressed as mean (SD) and median and 25–75 percentiles. EEG data and the coefficients of correlation, $R^2$, of the pharmacodynamic fits using one or two values for $k_e$ were compared using the Wilcoxon signed ranks test. Blood propofol concentrations at which EEG amplitudes in the four frequency bands from 0 to 20 Hz reach their maximum were compared using the Friedman test. $P<0.05$ was considered significant. The computer program SPSS for Windows version 6.13 was used for statistical calculations.

Results

Extradural analgesia was adequate in all patients (sensory level to cold: T9 (T12—T5), median and range). No patient developed bradycardia (<50 beats min$^{-1}$) or hypotension (lowering of systolic blood pressure by >25% from the average of the systolic blood pressures measured at hospital admission, on

Figure 2  Typical analogue EEG recordings of a patient (no. 6) at representative moments during the propofol infusion and emergence. First amplitude maximum, second amplitude maximum = times when maxima in the 11–15 Hz frequency band were reached: first, during infusion; second, during emergence.

Figure 3  Representative time course of EEG amplitude in four frequency bands in a patient (no. 9) in response to a 10-min infusion of propofol 0.5 mg kg$^{-1}$ min$^{-1}$. All four frequency bands show two amplitude maxima, one during the infusion and a second during emergence. In each frequency band, there is a difference in amplitude between the first amplitude maximum and the second. This patient was unresponsive from 2.5 min until 24.5 min after the start of the infusion. Frequency bands: ▲ = 6–10 Hz; □ = 16–20 Hz; ■ = 0–5 Hz; ○ = 11–15 Hz.
modelling, at the times when consciousness was lost and regained were 6.45 (5.87–7.01) and 0.85 (0.64–1.09) mg l$^{-1}$ respectively. The measured blood propofol concentrations in individual patients during the infusion and the first 25 min after the infusion are shown in figure 1. The calculated pharmacokinetic parameters are shown in table 1.

The awake EEG was characterized by predominant activity in the 8–14 Hz frequency range. The EEG pattern did not change after the onset of extradural analgesia, although amplitude in the high-frequency bands increased in the patients who were shivering. After the start of the infusion, the amplitude in the high-frequency bands increased initially. With further increases in blood propofol concentration the EEG slowed and amplitude decreased. At the end of the infusion, slow-wave activity was present with spindles of high-frequency activity.
activity. During emergence, high-amplitude high-frequency activity reappeared, followed by a decrease in amplitude until the patient became responsive (fig. 2).

Quantitatively, marked amplitude changes occurred in the frequency bands between 0 and 20 Hz, but amplitude in the frequency bands between 21 and 30 Hz was small and often contained obvious muscle artefacts when patients were responsive. Therefore data calculated from these bands were not used in the calculations and are not shown in the tables and figures. In all four frequency bands below 21 Hz, EEG amplitude showed a biphasic response to increase blood propofol concentration, that is, EEG amplitude initially increased and subsequently decreased to or beyond baseline values. When the infusion was stopped, EEG amplitude again showed a biphasic response: it increased to a maximum and then decreased until the patient became responsive (fig. 3).

The amplitude at the moment the patient became responsive was similar to or just above baseline values. The amplitude maxima reached during the infusion and during emergence were dissimilar in the 0–5 Hz and 11–15 Hz bands (table 2).

Table 2  EEG amplitude before, during and after a 10-min propofol infusion of 30 mg kg⁻¹ h⁻¹ and times of loss of responsiveness, maximum EEG amplitude, and return of responsiveness. *Different from baseline value; †different from maximum during infusion; ††different from the time of loss of responsiveness. Data are expressed as median and 25th–75th percentile

<table>
<thead>
<tr>
<th>Frequency band</th>
<th>0–5 Hz</th>
<th>6–10 Hz</th>
<th>11–15 Hz</th>
<th>16–20 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG amplitude (μV s⁻¹)</td>
<td></td>
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</tr>
<tr>
<td>Baseline</td>
<td>44 (24–69)</td>
<td>51 (19–76)</td>
<td>42 (17–53)</td>
<td>9 (2–27)</td>
</tr>
<tr>
<td>Loss of responsiveness</td>
<td>40 (35–62)</td>
<td>40 (31–54)</td>
<td>42 (32–71)</td>
<td>31* (7–38)</td>
</tr>
<tr>
<td>Maximum during infusion</td>
<td>87* (46–99)</td>
<td>43 (32–70)</td>
<td>86* (69–137)</td>
<td>52* (19–84)</td>
</tr>
<tr>
<td>End of infusion</td>
<td>126* (71–190)</td>
<td>71* (46–137)</td>
<td>106* (76–269)</td>
<td>54* (20–99)</td>
</tr>
<tr>
<td>Maximum during emergence</td>
<td>52* (29–119)</td>
<td>34 (24–123)</td>
<td>43 (23–210)</td>
<td>11 (4–20)</td>
</tr>
<tr>
<td>Time (min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loss of responsiveness</td>
<td>4.8†† (3.5–9.0)</td>
<td>6.0†† (4.0–8.5)</td>
<td>3.8 (1.5–8.0)</td>
<td>2.5†† (0.5–4.0)</td>
</tr>
<tr>
<td>Amplitude maximum during infusion</td>
<td>16.8 (10.5–20.8)</td>
<td>17.0 (11.5–20.8)</td>
<td>19.3 (15.3–24.8)</td>
<td>21.8 (14.6–30.5)</td>
</tr>
<tr>
<td>Return of responsiveness</td>
<td>16.8 (10.5–20.8)</td>
<td>17.0 (11.5–20.8)</td>
<td>19.3 (15.3–24.8)</td>
<td>21.8 (14.6–30.5)</td>
</tr>
</tbody>
</table>

Figure 5  Box plots of calculated blood propofol concentrations at the times of loss and regaining of responsiveness, and when EEG amplitude maxima were reached in the frequency bands 0–5, 6–10, 11–15, and 16–20 Hz during infusion and emergence. With increasing frequency the maxima occurred at lower blood concentrations. Box plots represent median, 25th–75th percentile, 10th–90th percentile, and lowest and highest values (open circles). *P < 0.01 compared with loss of responsiveness to verbal command. †P < 0.01 compared with return of responsiveness to verbal command.

Figure 6  Observed and estimated EEG amplitude in the frequency range 11–15 Hz vs time in patient no.7. Estimated values were obtained by fitting measured amplitudes to the Mandema biphasic pharmacodynamic model, allowing either one or two values for keo. o = observed effect. Allowing one keo resulted in identical maximal EEG amplitudes during and after infusion and an R² of 0.78 (thin line). Allowing two values for keo resulted in a smaller maximal EEG amplitude during infusion and an R² of 0.87 (thick line).
Loss of responsiveness occurred immediately after the initial amplitude maximum in the 16–20 Hz band and before or simultaneously with the initial amplitude maximum in the 11–15 Hz band. Patients regained consciousness after the second amplitude maximum in the 11–15 Hz band and the 16–20 Hz band. As the EEG amplitude had a biphasic response to blood propofol concentrations, responsiveness to verbal command could not be related to an amplitude value in any frequency band without information on the time course of the value.

Calculated pharmacodynamic parameters derived from EEG amplitudes in the 11–15 Hz band of individual patients allowing two values of $k_{eo}$ are shown in table 3.

The two-effect compartment model fitted the data significantly better than the one-effect compartment model in both the 11–15 Hz band and the 0–5 Hz band (median $R=0.88$ vs 0.79 in the 11–15 Hz band, and 0.78 vs 0.68 in the 0–5 Hz band, $P<0.01$). Figure 6 shows an example of the one- and two-compartment model fitted to the EEG data in the 11–15 Hz frequency band.

$E_{C_{50}}$ was higher in the 0–5 Hz band: 4.2 (3.2–4.5) mg l$^{-1}$ vs 3.6 (3.1–4.1) mg l$^{-1}$ in the 11–15 Hz band. In the 0–5 Hz band $k_{e1}$ was larger than $k_{e2}$: 0.27 (0.22–0.33) min$^{-1}$. In the 11–15 Hz band, however, $k_{e1}$ was smaller than $k_{e2}$: 0.16 (0.07–0.21) min$^{-1}$ vs 0.21 (0.16–0.25) min$^{-1}$.

**Discussion**

In this study, during a 10-min infusion of propofol, we observed a biphasic EEG amplitude response to an increasing blood propofol concentration in all frequency bands. EEG amplitude maxima were dissimilar during infusion and emergence in two of the four frequency bands. The blood propofol concentration at which the EEG amplitude maximum in a particular frequency band occurred was inversely related to the frequency of this band.

A biphasic EEG response to increasing propofol concentrations was first described by Hazeaux and colleagues, who reported an increase followed by a decrease in alpha amplitude, and the appearance of theta and delta activity after an injection of propofol 2.5 mg kg$^{-1}$ in 30 s. Bourgeois and co-workers described similar changes during induction of anaesthesia in children with a propofol bolus of 3 or 5 mg kg$^{-1}$. They found a transient shift from predominantly alpha (9–10 Hz) activity to beta (>14 Hz) activity, followed by continuous delta activity. Hazeaux and Bourgeat did not quantify the EEG changes or determine blood propofol concentrations at which these phenomena occurred. In the presence of sedative propofol blood concentrations, an increase in beta activity accompanied by an increased sedation level has been reported. In both studies, propofol was given in doses sufficient to achieve sedation, and the infusion rate was adjusted to prevent unconsciousness. Beta activity was increased throughout the procedure and showed no biphasic response, probably because the patients did not become unconscious and blood propofol concentrations were 0.69 (0.34) mg l$^{-1}$ and 1.14 (0.39) mg l$^{-1}$ in the presence of anaesthetic propofol concentrations, Schwinden and colleagues used the median frequency, calculated from the power spectrum, as the EEG effect parameter for closed-loop feedback control of propofol anaesthesia. They described a monophasic response to propofol, that is, a decrease of median frequency with increasing blood concentrations. More recently, Forrest and co-workers reported a biphasic shift of median frequency shortly after the start of a propofol infusion. These authors were unable to quantify the maximum in median frequency because they collected insufficient data in this concentration range.

The biphasic EEG amplitude response in the 11–15 Hz and the 16–20 Hz bands observed in the present study is consistent with the increased beta activity found by others during sedation, and the decreased median frequency described during anaesthetic propofol concentrations. Although we were unable to demonstrate an influence of extradural analgesia on the EEG in a previous study, in the present study we observed an increase in amplitude in the 16–20 Hz band. As shivering occurred in four patients, we suspect that this increase in amplitude in the 16–20 Hz band is the result of EMG artefact. EEG amplitude in the other frequency bands was not different from baseline values. The 30 Hz low-pass filter probably eliminates EMG artefacts caused by shivering in the other frequency bands. Although extradural analgesia has no effect on EEG amplitude itself, synergistic effects of extradural analgesia with propofol on the EEG amplitude cannot be excluded.
Extradural analgesia might have influenced the pharmacokinetics of propofol. Haemodynamic changes, venous pooling and hepatic blood flow can affect its distribution and clearance. In comparison with the pharmacokinetic data reported by other investigators, we observed a shorter and a smaller . In addition to the effects of extradural analgesia, a short sampling period may have been responsible for these differences. However, changes in pharmacokinetic parameters had no influence on the estimation of pharmacodynamic parameters, as measured blood propofol concentrations were used to calculate effect compartment concentrations.

The sigmoid model has been applied successfully for pharmacodynamic modelling of plasma concentration–effect relationships of opioids and hypnotics. However, modelling of biphasic effects remains a major challenge. One might transform EEG data in such a way that a sigmoid model fits the data. and colleagues suggested semilinear canonical correlation, which uses a summation of log-transformed EEG power in several frequency bins, which are multiplied by a weight factor to yield effect data. When we applied this method to our data, we achieved weight factors for individual patients that resulted in good fits in nine of the 10 . However, when the weight factors of all patients were averaged and the average weight factor was applied to the EEG data, the sigmoid model could not be fitted satisfactorily. have described the application of a nonparametric approach to characterize biphasic EEG effects in response to thiopentone in rats. The method describes the relationship between the concentration of drug in the effect compartment and distinct EEG effects including baseline effect, maximal effect, 50% of baseline effect, and burst suppression. However, nonparametric estimation of needed to calculate the effect site concentrations, is based on the assumption that the effect during increasing and decreasing effect compartment concentrations is similar. As the magnitude of EEG effects during and after the infusion in the present study was dissimilar in the 0–5 Hz band and the 11–15 Hz band, nonparametric estimation of and effect site concentrations was not possible. Accordingly, we did not attempt to use this method to model the effect of propofol.

It could be that we observed dissimilar EEG amplitude maxima during infusion and during emergence in the present study because the 15 s averaging epoch used was too long to detect a transient increase in amplitude in response to a rapidly changing propofol concentration. This could explain the lower effect compartment concentration in the 11–15 Hz band, when concentrations changed rapidly. However, the amplitude maximum in the 0–5 Hz band was highest during infusion, in spite of the same rapid concentration changes. Another argument against this explanation is that the amplitude maxima in the 11–15 Hz band did not change and remained smallest during infusion after reanalysis of the data using 2 s epochs.

The dissimilar EEG amplitude maxima during infusion and emergence suggest that more than one effect compartment may exist. One might hypothesise two compartments with different equilibration constants exerting opposing effects: inhibition and activation. Applying this concept to the EEG amplitude in, for example, the 11–15 Hz range results in the following sequence: during an increasing blood propofol concentration, the concentration will rise faster in the “inhibiting” effect compartment than in the “activating” compartment, and therefore inhibition will dominate soon after the start of drug administration. However, after stopping the propofol infusion, the concentration in the “inhibiting” effect compartment will decrease more rapidly, thus allowing the “activating” effect to become clinically apparent.

Because dissimilar effects during increasing and decreasing blood concentrations preclude modelling with nonparametric models, we chose the simplest parametric model proposed by (with the least number of parameters to be estimated) to fit our data. Although the model is a simplification of the summation of two sigmoid curves, it was possible to model the data consistently according to this method with good results.

The findings that using two values for resulted in significantly better fits than using one, and that there were significant differences between and supports the hypothesis that assuming two effect compartments with unequal equilibration constants might explain the dissimilar EEG amplitudes observed during infusion and emergence in the 0–5 Hz and the 11–15 Hz band.

One might hypothesise that differences in regional cerebral blood flow could be a physiological explanation for these differences. An alternative explanation might be that there are differences in the affinity or dissociation rate of propofol for receptors on either excitatory or inhibitory neurons. A third explanation might be that in either the excitatory or the inhibitory neuron, after initial occupation of the receptor, a secondary pathway must become activated, which requires additional time before an effect becomes apparent.

Because of the biphasic character of the EEG response to propofol, a particular EEG amplitude may correspond to more than one propofol concentration. This finding makes it difficult to use the EEG amplitude as an indicator of the level of consciousness. Estimation of the level of consciousness requires additional information about the time course of the EEG amplitude and the time course of the EEG amplitude in other frequency bands. For use as a control parameter of the level of consciousness one might try to maintain the EEG amplitude in the 0–5 Hz band at its maximal value, as these maxima correspond to propofol concentrations at which patients are unresponsive. When EEG amplitude decreases from the maximal value one can determine the direction of change of propofol concentration from the changes of EEG amplitudes in other frequency bands.

In conclusion, the propofol concentration—EEG effect relationship is biphasic in all EEG frequency bands. The present study demonstrates that the EEG effects during infusion and emergence are dissimilar, which suggests the existence of at least two effect
compartments with different equilibration constants exerting opposing effects on EEG amplitude. Modelling of the blood propofol concentration—EEG relationship was possible using a biphasic parametric model.

Acknowledgements

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References