Prediction of Movement during Propofol/Nitrous Oxide Anesthesia

Performance of Concentration, Electroencephalographic, Pupillary, and Hemodynamic Indicators


Background: Movement in response to painful stimulation is the end point classically used to assess the potency of anesthetic agents. In this study, the ability of modeled propofol effect-site concentration to predict movement in volunteers during propofol/nitrous oxide anesthesia was evaluated, then it was compared with the predictive abilities of the Bispectral Index and 95% spectral edge frequency of the electroencephalogram, pupillary reflex amplitude, and systolic arterial blood pressure. In addition, the relationships between simple end points of loss and recovery of consciousness, and pupillary, hemodynamic, and propofol concentration indicators were studied.

Methods: Ten healthy volunteers were anesthetized with an infusion of propofol, which was increased in three equal steps to 21 mg·kg lean body mass\(^{-1}\)·h\(^{-1}\). After loss of the ability to hold a syringe and of the eyelash reflex, 60% nitrous oxide was introduced and the trachea was intubated without the use of muscle relaxants. The propofol infusion rate then was decreased to 15.4 mg·kg lean body mass\(^{-1}\)·h\(^{-1}\). Ten minutes later, tetanic electrical stimulation was administered to the thigh via needle electrodes: if movement was observed within 1 min, the propofol infusion rate was increased by 1.75 mg·kg lean body mass\(^{-1}\)·h\(^{-1}\) 5 min after the stimulus; if not, it was similarly decreased. This 15-min sequence was repeated until volunteers “crossed over” from movement to no movement (or vice versa) four times. The propofol infusion rate then was increased to 21 mg·kg lean body mass\(^{-1}\)·h\(^{-1}\), nitrous oxide was discontinued, the trachea was extubated, and the infusion rate was decreased in five equal steps over 50 min. The times at which the eyelash reflex returned and the birth date was recalled were recorded. The electroencephalogram was monitored continuously (FP1, FP2, ref: nasion, ground: mastoid). Measurements of the pupillary response, arterial blood pressure, and heart rate were recorded during induction and awakening, just before and for 5 min after each stimulation. Arterial blood samples were obtained for propofol assay, and propofol effect-site concentrations were calculated at each time. The predictive value of indicators was compared using a new statistic, the prediction probability (P\(_{\text{Pr}}\)).

Results: Loss and return of the eyelash reflex occurred at greater propofol effect-site concentrations than either dropping the syringe or recall of the birthday. The propofol effect-site concentration (in the presence of 60% nitrous oxide) predicted to prevent movement after a supramaximal stimulus in 50% of volunteers was 1.80 mg/ml (95% confidence limits: 1.40–2.34 mg/ml). The Bispectral Index (P\(_{\text{BI}}\) = 0.86), 95% spectral edge frequency (P\(_{\text{SEF}}\) = 0.81), pupillary reflex amplitude (P\(_{\text{PR}}\) = 0.74), and systolic arterial blood pressure (P\(_{\text{SBP}}\) = 0.78) did not differ significantly from modeled propofol effect-site concentration (P\(_{\text{Pr}}\) = 0.76) in their ability to predict movement.

Conclusions: Indicators of pharmacodynamic effect, such as the electroencephalogram, pupillary light reflex, and systolic arterial blood pressure, predict movement as well as effect-
site concentration during propofol/nitrous oxide anesthesia. Loss and return of the eyelash reflex correspond to a deeper level of anesthesia than syringe-dropping or recall of the birth date. (Key words: Anesthetics, gases: nitrous oxide. Anesthetics, intravenous: propofol. Depth of anesthesia, monitoring: Bispectral Index; electroencephalography; hemodynamics; pupillometry. Pharmacodynamics: effect-site concentration; propofol.)

MOVEMENT in response to painful stimulation is the end point classically used to assess the potency of anesthetic agents. Movement is easily defined and observed, and in its absence recall of intraoperative events by nonparalyzed patients is rare. However, anesthetic management often includes administration of muscle relaxants, precluding the routine use of movement as an indication to increase depth of anesthesia. Prediction of movement in paralyzed patients thus requires a monitor of anesthetic depth correlating with the probability of movement.

Hemodynamic indices predict neither movement nor intraoperative awareness. Power spectral analysis of the electroencephalogram (EEG) has some predictive value, but the relationship between EEG parameters and the likelihood of movement is not constant over a range of anesthetic conditions or drugs.

Recently, another EEG indicator, the Bispectral Index, was proposed as a measure of anesthetic depth, and proved retrospectively predictive of movement in response to surgical incision during isoflurane. ISOFLUORANE/ALFENTANIL, ISOFLOURANE/PROPFOF/NITROUS OXIDE anesthesia. This index quantifies the nonlinear relationships between EEG component waves, as well as analyzing the frequency and amplitude of EEG component waves. Thus, bispectral analysis can determine whether phase-coupled harmonic frequency components are present, whereas power spectral analysis cannot. The presence of such harmonics indicates increased synchronization of the EEG.

The pupillary light reflex is an indicator of anesthetic depth that now can be precisely quantified using a portable infrared pupillometer. Using this device, we have shown that pupillary responses correlate well with isoflurane and enflurane concentration. Whether this reflex response also can be used to predict movement remains unknown.

End-tidal concentration predicts movement in patients given volatile anesthetics. Concentration is both a measurable and reliable indicator because of the ease with which alveolar concentrations are established, maintained, and monitored, the reliability of the relationship between alveolar and brain concentrations, and the steepness of the population dose-response curves for these agents.

Although the short blood–brain equilibrium time and rapid onset and elimination of propofol suggest that blood concentration might predict movement during anesthesia, use of modeled effect-site concentration avoids the hysteresis between blood and the site of action of propofol when non–steady-state conditions exist. This may improve the ability to predict the likelihood of movement. Although propofol effect-site concentration cannot be measured in a clinically relevant time frame, it can be estimated from the infusion rate of computer-controlled infusion pumps, which incorporate pharmacokinetic data and effect-site equilibrium times. We therefore tested the hypothesis that during propofol/nitrous oxide anesthesia, indices of pharmacodynamic effect (the Bispectral Index, 95% spectral edge frequency, pupillary reflex amplitude, and systolic arterial blood pressure) are as accurate as propofol effect-site concentration in predicting movement after a supramaximal stimulus. In addition, we studied the relationships between simple end points of loss and recovery of consciousness and pupillary, hemodynamic, and propofol concentration indicators.

Methods

With approval from the Committee on Human Research at the University of California, San Francisco, we studied ten healthy volunteers aged 25 ± 4 yr (mean ± SD), weighing 66 ± 15 kg, and with a lean body mass (LBM) of 50 ± 11 kg. Lean body mass was determined from height (cm) and weight (kg) using a formula:

females: LBM = (1.07 · weight) - [148 · (weight/height)²];
males: LBM = (1.10 · weight) - [128 · (weight/height)²].
Protocol

Lactated Ringer's solution was infused at 120 ml/h. A computerized anesthesia machine (Modulus CD, Ohmeda, Madison, WI) was used to monitor heart rate, oxygen saturation, and end-tidal gas concentrations. These were recorded directly using automatic record-keeping software (IdaCare, Premier Anesthesia Systems, Atlanta, GA). Arterial blood pressure was measured directly in the radial artery of the nondominant arm.

Anesthesia was induced with propofol (Zeneca Pharmaceuticals Group, Wilmington, DE) using an infusion pump (Ohmeda). The infusion rate was increased in three 10-min steps from 0 to 21 mg·kg LBM⁻¹·h⁻¹. After loss of consciousness, 60% nitrous oxide in oxygen was administered, and airway support was provided as necessary. Before induction, volunteers were asked to grasp a 20-ml plastic syringe firmly between the thumb and forefinger of one hand. Dropping the syringe and loss of the eyelash reflex were used to indicate loss of consciousness.

Thirty minutes after the propofol infusion was started, the trachea of each volunteer was intubated without administration of muscle relaxants. If coughing or movement was observed, an intravenous bolus of 20–40 mg propofol was administered. Because substantial movement was observed in the first four subjects, we altered the protocol to include 40 mg intravenous propofol immediately before intubation in the remaining volunteers. The lungs then were mechanically ventilated to maintain an end-tidal carbon dioxide partial pressure of 35–40 mmHg.

After intubation, the propofol infusion rate was decreased to 15.4 mg·kg LBM⁻¹·h⁻¹, and kept constant for 15 min. An electrical stimulus was applied at 10 min, and volunteers' responses were observed for 5 min. Electrical stimuli were administered via 25-G needles placed intradermally on the left thigh and consisted of a 65- to 70-mA, 100-Hz electric current lasting 10 s. A positive response was defined as gross movement of the right leg, arms, or head within the first minute after stimulation. To prevent desensitization at the needle insertion site, the electrodes were moved 1 cm cephalad after each stimulation.

At the end of the 15-min test period, the infusion rate was changed and the protocol was repeated. The infusion rate was increased by 1.75 mg·kg LBM⁻¹·h⁻¹ when movement occurred, and similarly decreased when it did not. These up-and-down sequences were continued until volunteers "crossed over" from movement to nonmovement (or vice versa) four times, or 7 h of anesthesia elapsed.

The propofol infusion rate then was increased to 21 mg·kg LBM⁻¹·h⁻¹, nitrous oxide discontinued, the endotracheal tube removed, and oxygen administered. The propofol infusion rate was decreased to zero over a 50-min period in 10-min steps. The times at which the eyelash reflex returned and volunteers were able to recall their birthdays were recorded.

To avoid any confounding effect of hypothermia, distal esophageal temperature was maintained between 36 and 37°C using a Bair Hugger forced-air warming cover positioned over the legs (model 300 cover, model 200 blower, Augustine Medical, Eden Prairie, MN).¹²

Measurements

Pupillary reflexes were evaluated using a portable infrared pupillometer (Fairville Medical Optics, Larkings Green, Amersham, England), as described previously.¹² The instrument was programmed to search for a stable pupillary diameter, flash a 0.5-s light stimulus, and initiate a 2-s, 10-Hz scan at the start of the stimulus. All measurements were taken from the right eye and ambient light was excluded from the left eye.

The EEG was recorded continuously during each study. After preparation of the skin, gold cup electrodes were filled with conductive paste and attached to the skin with adhesive. The electrodes were positioned at FP1 and FP2, with the reference electrode at the nasion and the ground electrode at the mastoid. A microprocessor-based, four-channel monitor (B500, Aspect Medical Systems, Natick, MA) was used to collect raw EEG data, which were recorded for off-line analysis (Version 3.0) by Aspect Medical Systems.

Electroencephalographic data were acquired in 4-s epochs, with each successive epoch overlapping the previous one by 3 s. After rejection of spurious data due to artifact, both the power spectrum and the bispectrum of each epoch were calculated. Individual power spectral parameters from the last 60 epochs were averaged together. High and low cutoff frequencies were 30 Hz and 0.5 Hz, respectively. The relative power spectral parameters calculated were the delta power (0.5–3.75 Hz), theta power (4.0–7.75 Hz), alpha power (8.0–13.5 Hz), beta power (13.75–30.0 Hz), 95% spectral edge, and median frequencies. The bispectra of 60 successive epochs were averaged and a series of intermediate bispectral parameters were computed from the averaged bispectrum. These inter-

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mediate parameters were combined into a multivariate Bispectral Index using coefficients developed on a separate EEG database that did not include the present subjects. Processed data from the two frontal channels were combined and saved every 15 s.

During each 15-min infusion, samples of arterial blood were obtained at 9 elapsed min in all volunteers. Samples also were obtained at 14 min in the first three volunteers, to assess the constancy of propofol blood concentrations during stimulation. They were placed in heparinized tubes and stored at 4°C for up to 6 weeks (propofol blood concentrations decrease less than 0.2%/week at 4°C). Samples were analyzed using a high-performance liquid chromatography assay, modified from the method of Plummer. Effect-site concentrations were calculated by convolving the plasma concentrations over time against the function, $k_{\text{eq}}e^{-k_{\text{eq}}t}$, the disposition function of the effect site. The convolution interpolated adjacent plasma concentrations, assuming a linear rise when plasma concentrations were increasing, and a log-linear fall when plasma concentrations were decreasing. A value of 0.239 min$^{-1}$ was taken as the $k_{\text{eq}}$. Theoretical background for these calculations is provided by the work of Verotta and Sheiner. The relationships between movement in response to electrical stimulation and EEG, pupillary, hemodynamic, and propofol concentration data were defined using logistic regression (BMDP Statistical Systems, Los Angeles, CA and SPSS, Chicago, IL). Responses to the first three stimuli in each volunteer were not included in analysis, to exclude the effect of changing the protocol to include a 40-mg bolus of propofol before intubation. The remaining 130 stimuli were used for analysis. Logarithmic transformation of propofol blood and effect-site concentration, relative beta power, and median frequency was performed before analysis. Individual logistic curves were obtained for each volunteer, as well as an overall curve obtained by performing logistic regression on all 130 stimulus values. For the latter, the standard errors of the estimate, provided by BMDP for the variable values at the 50% and 95% nonresponse levels, were based on the assumption that the 130 stimuli were independent. These standard errors of the estimate were used to compute the 95% confidence limits. The significance value for the SPSS statistic “—2 log likelihood” was used as a measure of logistic curve fit. This significance value is obtained for the null hypothesis that the logistic curve explains the quantal data perfectly, that is, that the likelihood equals one. A larger significance value corresponds to a better logistic curve fit. See Smith et al. for a further discussion of this measure.

Ability of propofol concentration, EEG, pupillary, and hemodynamic indicators to predict movement was evaluated using prediction probability ($P_k$), which compares the performance of indicators having different units of measurement. The mathematical basis of $P_k$ was described by Smith et al. Numerically, $P_k$ is the probability that an indicator predicts correctly which of a pair of randomly selected stimuli, one causing movement and the other not, will cause movement. An indicator that predicts perfectly whether a movement response will occur has a $P_k$ value of 1.0, whereas an indicator that performs no better than chance has a

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Data Analysis

A single measurement of arterial blood pressure and heart rate was recorded at each time. Electroencephalographic data sets collected 60 s before painful stimulation were used in the prediction of movement analysis. Electroencephalographic data collected during induction and awakening were not analyzed because EEG activation at low anesthesia concentrations may complicate interpretation of results. Three sets of pupillary data were averaged, producing one averaged scan from which pupillary parameters were recorded for volunteers at each time during induction and awakening, and before stimulation. To determine the response of indicators to painful stimulation, pupillary and EEG data collected at $+1.5$, $-0.5$, $0$, $0.33$, $0.66$, $1.5$, $2.5$, $3.5$, and $4.5$ min were analyzed.

To determine the value of each indicator for identifying loss of consciousness as defined by the dropping of the syringe, loss and return of the eyelash reflex, and ability to recall birth date, we used repeated-measures analysis of variance and Scheffé’s $F$ tests.

Electroencephalographic, pupillary, and hemodynamic data collected just before and for 5 min after each stimulus were analyzed using repeated-measures analysis of variance and Dunnett’s tests. Paired $t$ tests were used to compare the indicator data obtained when volunteers moved and did not move.

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$P_k$ value of 0.5. Values for $P_k$ for an indicator were computed for each volunteer, and an average of these $P_k$ values then was calculated. A value of $P_k$ also was computed for all 130 stimuli combined, and the jackknife method was used to compute the standard error of the estimate,\(^\text{19}\) based on the assumption that the 130 stimuli were independent.

The predictive performance of effect-site concentration was compared to the Bispectral Index, 95% spectral edge frequency, pupillary reflex amplitude and systolic arterial blood pressure. First, a Wilcoxon test was used to determine whether the individual-subject $P_k$ values for the alternative indicators differed from those for effect-site concentration. Individual-subject $P_k$ values for an indicator express the indicator's ability to predict a response if a subject's individual response curve is known. Second, a paired-data jackknife analysis\(^\text{19}\) was used to determine whether combined-subject $P_k$ values for alternative indicators differed from the combined-subject $P_k$ value for effect-site concentration. Performance, as measured by the combined subject $P_k$, is of interest if the population response curve is known, but the individual-subject response curves are not (as is typically the case). For multiple comparisons, we used the Bonferroni method, as modified by Holm.\(^\text{20}\)

Results are presented as mean ± SD, except for the logistic curve 50% and 95% nonresponse levels, which are presented as estimate ± standard error of the estimate. $P < 0.05$ was considered statistically significant.

**Results**

Induction of anesthesia was smooth in all cases and no excitatory movements were observed. Recovery from anesthesia was similarly uneventful.

Pupillary, hemodynamic, and propofol concentration indicators during loss and return of consciousness changed in a sequence, consistent with gradually increasing anesthetic depth during induction and decreasing anesthetic depth during awakening. The volunteers were still awake when the syringe was dropped but not when the eyelash reflex was lost.

Loss and return of the eyelash reflex occurred at greater propofol effect-site concentrations than either dropping the syringe or recall of the birth date. Initial pupillary diameter was smaller when the eyelash reflex was lost than when it was regained: the other parameters did not differ significantly at the two times. The pupillary reflex had returned to normal by the time volunteers could recall their birth date, but they remained drowsy, and this sedation was reflected by residual blood propofol concentrations (table 1).

Non-response levels were defined by the fraction of volunteers predicted not to move at a particular blood or effect-site concentration, or value of an EEG, pupillary or hemodynamic indicator (table 2). The propofol effect-site concentration at the 50% nonresponse level ($C_p,50$) was 1.8 µg/ml (95% confidence limits: 1.4–2.3 µg/ml; fig. 1). To prevent movement on 95% of occasions ($C_p,95$) a predicted effect-site concentration of 9.7 µg/ml (±8–19.4 µg/ml) would be required. Comparable values for propofol blood concentration were 1.7 µg/ml (1.2–2.3 µg/ml) and 12.3 µg/ml (5.1–29.6 µg/ml) respectively. The predicted systolic arterial blood pressure at the 95% non-response level was 74 mmHg (64–83 mmHg; fig. 2), a 50% decrease from its pre-induction value. Data for the Bispectral Index, 95% spectral edge frequency and pupillary reflex amplitude are presented in figures 3–5.

Prediction probability ($P_k$) values were calculated to determine the relative performance of the EEG, pupillary, hemodynamic and concentration indicators (table 2). The $P_k$ value (based on all 130 stimuli) for propofol effect-site concentration was 0.76 and for blood concentration, 0.74. In contrast, the Bispectral Index had a $P_k$ of 0.86, and 95% spectral edge frequency, 0.81. Median frequency and relative beta power also had $P_k$ values exceeding 0.80. When compared to the effect-site concentration, however, no indicator proved significantly different. All indicators, with the exception of heart rate, predicted movement after painful stimulation significantly better than chance alone. When $P_k$ was calculated using the individual values in each volunteer, prediction improved. However, no significant differences in performance were demonstrated between effect-site concentration and bispectral index, 95% spectral edge frequency, pupillary reflex amplitude or systolic arterial blood pressure. A similar analysis performed using propofol blood concentration instead of effect-site concentration produced the same result, except that the Bispectral Index was significantly different from blood concentration (in the direction of improved prediction) in the paired-data jackknife comparison of combined-subject $P_k$ values.

The responses of representative indicators to painful stimulation are shown in figure 6. At each measurement time, most indicator values were significantly greater in volunteers who moved than in those who did not.
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Table 1. Prediction of Loss of Consciousness and Awakening during Propofol Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Syringe Dropped</th>
<th>Eyelash Reflex Lost</th>
<th>Eyelash Reflex Regained</th>
<th>Birth Date Recalled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood propofol (µg/ml)</td>
<td>0</td>
<td>1.86 ± 0.83</td>
<td>2.89 ± 0.72*</td>
<td>1.91 ± 0.67</td>
<td>1.72 ± 0.57</td>
</tr>
<tr>
<td>Effect-site propofol (µg/ml)</td>
<td>0</td>
<td>1.21 ± 0.56†</td>
<td>2.12 ± 0.71</td>
<td>2.31 ± 0.52</td>
<td>1.97 ± 0.43</td>
</tr>
<tr>
<td>SABP (mmHg)</td>
<td>136 ± 15</td>
<td>110 ± 19</td>
<td>100 ± 17</td>
<td>115 ± 9</td>
<td>115 ± 10</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>76 ± 16</td>
<td>73 ± 11</td>
<td>74 ± 10</td>
<td>78 ± 9</td>
<td>79 ± 11</td>
</tr>
<tr>
<td>Initial diameter (mm)</td>
<td>6.4 ± 0.8</td>
<td>5.7 ± 1.2</td>
<td>3.8 ± 0.6*</td>
<td>5.7 ± 1.2</td>
<td>5.8 ± 1.0</td>
</tr>
<tr>
<td>Reflex amplitude (mm)</td>
<td>2.0 ± 0.4</td>
<td>1.9 ± 0.6</td>
<td>1.3 ± 0.5†</td>
<td>1.7 ± 0.4</td>
<td>2.1 ± 0.4</td>
</tr>
<tr>
<td>Constriction velocity (mm/s)</td>
<td>6.2 ± 1.6</td>
<td>6.0 ± 1.6</td>
<td>5.1 ± 1.9</td>
<td>4.6 ± 1.2</td>
<td>6.0 ± 1.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
SABP = systolic arterial blood pressure. Repeated measures ANOVA with Scheffé’s F test (P < 0.05).
* Different from control, syringe dropped, eyelash reflex regained, and birth date.
† Different from control, eyelash reflex lost, eyelash reflex regained and birth date.
‡ Different from control, syringe dropped, and birth date.

The pupillary reflex amplitude and systolic arterial blood pressure changed statistically significantly after stimulation. Pupillometry demonstrated the most dramatic response. There was swift dilatation of the pupil, which was similar in magnitude in both groups, but sustained longer in those who moved than in those who did not. The increase in systolic arterial blood pressure after stimulation was statistically significant, but not clinically important. The Bispectral Index and 95% spectral edge frequency did not change significantly after painful stimulation. Heart rate did not differ significantly between those who moved and those who did not; nor did heart rate increase after stimulation.

We assessed differences between propofol blood concentrations at 9 and 14 elapsed min of the 15-min constant-rate infusions in the first three volunteers (48

Table 2. Prediction of Movement during Propofol/Nitrous Oxide Anesthesia: Nonresponse Levels and P₀ Values

<table>
<thead>
<tr>
<th></th>
<th>50% Nonresponse Level</th>
<th>95% Nonresponse Level</th>
<th>Significance*</th>
<th>P₀ (all 130 stimuli)</th>
<th>P₀ (average of individual P₀s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood propofol (µg/ml)</td>
<td>1.70 (1.24–2.32)</td>
<td>12.28 (5.10–29.62)</td>
<td>0.07</td>
<td>0.74 ± 0.05</td>
<td>0.83 ± 0.11</td>
</tr>
<tr>
<td>Effect-site propofol (µg/ml)</td>
<td>1.81 (1.40–2.34)</td>
<td>9.65 (4.81–19.38)</td>
<td>0.11</td>
<td>0.76 ± 0.05</td>
<td>0.88 ± 0.11</td>
</tr>
<tr>
<td>Bispectral index</td>
<td>57.3 (54.1–60.5)</td>
<td>37.6 (31.3–43.9)</td>
<td>0.80</td>
<td>0.86 ± 0.03</td>
<td>0.87 ± 0.13</td>
</tr>
<tr>
<td>Relative delta power (%)</td>
<td>46.7 (39.8–53.7)</td>
<td>92.5 (76.3–108.7)</td>
<td>0.28</td>
<td>0.79 ± 0.04</td>
<td>0.83 ± 0.19</td>
</tr>
<tr>
<td>Relative beta power (%)</td>
<td>12.6 (9.8–16.2)</td>
<td>2.6 (1.5–4.5)</td>
<td>0.50</td>
<td>0.83 ± 0.04</td>
<td>0.92 ± 0.08</td>
</tr>
<tr>
<td>95% SEF (Hz)</td>
<td>18.5 (17.0–19.5)</td>
<td>12.7 (10.6–14.8)</td>
<td>0.35</td>
<td>0.81 ± 0.04</td>
<td>0.89 ± 0.15</td>
</tr>
<tr>
<td>Median frequency (Hz)</td>
<td>5.3 (4.2–6.8)</td>
<td>1.1 (0.6–1.9)</td>
<td>0.39</td>
<td>0.80 ± 0.04</td>
<td>0.86 ± 0.17</td>
</tr>
<tr>
<td>SABP (mmHg)</td>
<td>100 (96–104)</td>
<td>74 (64–83)</td>
<td>0.32</td>
<td>0.78 ± 0.04</td>
<td>0.81 ± 0.25</td>
</tr>
<tr>
<td>Reflex amplitude (mm)</td>
<td>0.4 (0.3–0.5)</td>
<td>0.0 (0–0.2)</td>
<td>0.16</td>
<td>0.74 ± 0.05</td>
<td>0.76 ± 0.17</td>
</tr>
<tr>
<td>Constriction velocity (mm/s)</td>
<td>1.9 (1.7–2.1)</td>
<td>0.6 (0.2–1.1)</td>
<td>0.43</td>
<td>0.80 ± 0.04</td>
<td>0.81 ± 0.13</td>
</tr>
</tbody>
</table>

SEF = spectral edge frequency; SABP = systolic arterial blood pressure. Nonresponse levels presented as value (95% confidence limits); P₀ (all 130 stimuli) presented as estimate ± standard error of the estimate (P₀ average of individual P₀s) presented as mean ± SD.
* Significance value for the SPSS statistic “–2 log likelihood” corresponding to the null hypothesis that the logistic curve explains the quantal data perfectly, i.e., that the likelihood equals 1. A larger significance value means a better fit of the logistic curve to the data.

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ampplitude, and systolic arterial blood pressure, predict movement as well as propofol effect-site concentration in healthy volunteers administered propofol/nitrous oxide anesthesia.

Systolic arterial blood pressure performed surprisingly well as a predictor of movement in these controlled circumstances. However, the effects of disease, surgery, fluid administration, and drugs affecting the circulation are likely to reduce the predictive value of arterial blood pressure in the clinical setting. Administration of opioids may similarly reduce the performance of the pupillary light reflex.

The generally steeper slopes of the individual logistic curves compared to the curve generated by analyzing all 130 stimuli together indicates that knowing the responsiveness of a person facilitates prevention of

Discussion

This study demonstrates that indices of pharmacodynamic effect, such as the Bispectral Index and 95% spectral edge frequency of the EEG, pupillary reflex

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Fig. 3. Percentage of volunteers not responding with movement after painful stimulation versus Bispectral Index. In the upper part of the figure, each dot represents a stimulus. In the lower part, the bold curve represents all 130 stimuli combined, with 95% confidence limits at the 50% and 95% nonresponse levels. The other curves represent individual volunteers.

movement and provision of adequate anesthesia in that person, even though such individual “calibration” rarely is available clinically. The benefit of knowing individual responsiveness is quantified by the amount to which average individual-subject $P_k$ values exceed the overall combined-subject $P_k$ value.

The propofol blood concentration at which 50% of volunteers were predicted to move after supramaximal electrical stimulation ($C_{p50}$) was 1.70 μg/ml (95% confidence limits: 1.24–2.32 μg/ml). This finding was consistent with values previously reported during propofol/nitrous oxide anesthesia: 1.66 μg/ml during propofol/nitrous oxide/morphine anesthesia and 2.5 μg/ml during propofol/nitrous oxide/lorazepam anesthesia. In contrast, the $C_{p50}$ of propofol alone reportedly is 15.2 μg/ml.

No indicator we studied perfectly predicted movement after supramaximal electrical stimulation. There are several possible explanations for this lack of predictive value that relate to propofol’s pharmacokinetics and pharmacodynamics. To eliminate the confounding effects of pharmacokinetic variability in the response of subjects to a stimulus, constant blood concentrations and blood-to-effect-site equilibration are required. Constant-rate infusions, such as those used in this study, result in exponentially declining rates of rise or fall in drug concentration, and potentially may introduce error. We took advantage of the near steady-state concentrations toward the end of each step, and were able to maintain reasonably constant propofol blood concentrations between 9 and 14 min (as evidenced by data from the first three volunteers). As electrical stimulation was applied at 10 min, we expect that propofol blood concentration changed even less between 9 and 10 min, than between 9 and 14 min. Smith et al. used

Fig. 4. Percentage of volunteers not responding with movement after painful stimulation versus 95% spectral edge frequency. In the upper part of the figure, each dot represents a stimulus. In the lower part, the bold curve represents all 130 stimuli combined, with 95% confidence limits at the 50% and 95% nonresponse levels. The other curves represent individual volunteers.
only preassessment and postassessment samples which were within ±35% of each other for their determination of propofol Cₜ₀; all our sample pairs fell within these boundaries. The homogeneous nature of our study group, and the use of lean body mass to calculate dosage,²⁰ probably contributed to the observed relatively constant levels.

To account for effect-site equilibration in a series of exponentially changing rates of increase or decrease in blood concentration,²⁷ we calculated predicted effect-site concentrations, using a kₑ₀ = 0.239 min⁻¹ (t₁/₂ₑ₀ = 2.9 ± 2.2 min). This value was calculated by Schuttler et al. using the EEG median frequency. The assumptions inherent in this analysis that may introduce error are: (1) the plasma concentration versus time curves in our volunteers roughly captured the shape of the curves in the model, which assumed a linear

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**Fig. 5.** Percentage of volunteers not responding with movement after painful stimulation versus pupillary reflex amplitude. In the upper part of the figure, each dot represents a stimulus. In the lower part, the bold curve represents all 130 stimuli combined, with 95% confidence limits at the 50% and 95% nonresponse levels. The other curves represent individual volunteers.

**Fig. 6.** Response to painful stimulation. SEF = spectral edge frequency; Amp = amplitude; BP = blood pressure. Elapsed time zero identifies stimulus. Most indicator values were significantly greater in volunteers who moved than in those who did not. The pupillary reflex amplitude and systolic arterial blood pressure changed significantly after stimulation. Data are presented as means ± SD.

**Fig. 7.** Arterial blood sampled at 9 and 14 min of each 15-min cycle was analyzed in the first three volunteers (n = 48). Effect-site propofol concentration at each time was modeled. No propofol blood concentration at 14 min differed from that at 9 min by more than 34%.
rather than log-linear rise; (2) the effect-site concentration was related to the plasma concentration by a first-order process; (3) the EEG median frequency reflected propofol’s action at its effect site; and (4) the intersubject and intrasubject variability in $k_{eo}$ was low. Intersubject and intrasubject variability in $k_{eo}$ is likely with propofol, given the large standard deviation in $t_{1/2eo}$, and is known to exist for other intravenous anesthetics. In addition, variability in the interaction of the anesthetic molecule with its site of action, the time between interaction and effect, and the magnitude of that effect, all may reduce $k_{eo}$ prediction accuracy. Indicators of pharmacodynamic effect, such as EEG, pupillary, and hemodynamic parameters, predict response from actual central nervous system activity and therefore remove the effect of intersubject or intrasubject variability. We were unable, however, to demonstrate that the performance of such indicators was statistically superior to calculated effect-site concentration.

Imperfect prediction by any one indicator in our study may reflect involvement of more parts of the central nervous system than were measured. Electroencephalographic measures, which reflect cortical activity, also failed to predict movement perfectly during thiopental anesthesia in humans and isoflurane anesthesia in rats. As the origin of movement in response to painful stimulation during anesthesia apparently is below the cortex, measures of brain stem or spinal cord function might perform better. However, in this study, hemodynamic and pupillary indicators were not superior to EEG. A multivariate analysis may have achieved better prediction.

Another reason for the imperfect prediction of the EEG relates to a possible biphasic effect of propofol on the EEG. Initially, activation occurs, with an increase in power in the beta range (propofol blood concentration: 1–2 $\mu$g/ml), depression, and finally burst suppression follow. There is a problem therefore interpreting the meaning of a particular value of an EEG indicator, because one indicator value may result from two different propofol concentrations. For this reason, EEG values at end points of induction and awakening were not reported, because propofol concentrations at these times were in the potentially biphasic range. During the stimulation phase of this study, however, propofol concentrations generally were greater than 1.5 $\mu$g/ml (i.e., in the linear part of the concentration/effect relationship). In addition, we used nitrous oxide as well as propofol, which likely results in a greater depth of anesthesia: deeper than the biphasic range. Despite potential problems, EEG indicators proved predictive of movement.

The frontal leads are appropriate for monitoring EEG changes during propofol anesthesia. The reference electrode is not usually positioned at the nasion because this site is susceptible to interference from facial movement. However, both the frontal leads and the nasion are convenient locations for electrode placement, especially during cranial surgery. The EEG performed well as a predictor of movement, despite this montage.

A constant, supramaximal stimulus is essential to the determination of anesthetic potency. Previous studies demonstrated that tetanic stimulation of the magnitude we applied is supramaximal. Recently, Laster et al. reported that electrical stimulation gave results comparable to tail clamp in rats given volatile anesthesia: only a 40-V stimulus produced a minimum alveolar concentration value significantly greater than tail clamp. We used the 15-V stimulus pattern of Laster et al., stimulus intensity was the same on each occasion, and the stimulating needles were moved after administration of each tetanic stimulation to avoid desensitization of nerve endings. We conclude, as did Laster et al., that, while electrical stimulation potentially is not supramaximal, it may be used as a substitute for conventional forms of stimulation in volunteers.

Using multiple identical stimuli in each volunteer, while economical, may result in intravolunteer correlation between stimuli, as described earlier. We potentially introduced error into our results by assuming, as have others, that each measurement in each volunteer was independent. Logistic regression and the $P_k$ statistic make the assumption of independent data; no comparable statistic has been developed that specifically permits nonindependent data. The assumption of independent data may have led to optimistic bias (underestimation) of confidence intervals for the 50% and 95% nonresponse levels and the standard errors of $P_k$ (all 130 stimuli). The removal of optimistic bias could only strengthen our result that there were no significant differences in performance between effect-site concentration and Bispectral Index, 95% spectral edge frequency, pupillary reflex amplitude, or systolic arterial blood pressure.


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Pupillary indicators revealed a more dramatic response to painful electrical stimulation than hemodynamic indicators, confirming our earlier observations. In addition, the response of the EEG was attenuated compared to the pupillary light reflex. Time averaging of the EEG data may be responsible for the apparent lack of EEG response.

Simple indicators of loss of consciousness, such as dropping a syringe and loss of the eyelash reflex, are used in studies of anesthetic induction. We demonstrated in this study that loss and return of the eyelash reflex correspond to a deeper level of anesthesia than syringe-dropping or recall of the birth-date. The pupillary light reflex was most useful in predicting that a particular level of anesthesia had been attained. Propofol blood concentrations in this study at the time the eyelash reflex was lost (2.9 ± 0.7 µg/ml) are similar to those reported previously (2.8 ± 0.6 µg/ml) and also are similar to concentrations when loss of responsiveness occurs during slow infusions. Despite the slow changes in propofol blood concentration during induction and recovery, blood-to-effect site hysteresis still was observed. Elimination of hysteresis in blood concentration between loss and return of the eyelash reflex demonstrates the utility of estimating effect-site concentration.

The same indicators of anesthetic effect used during induction often are used during recovery. Return of the eyelash reflex in our volunteers corresponded to return of a responsive state. Volunteers were oriented to time at greater propofol concentrations than reported previously, although administration of benzodiazepines and opioids in previous studies may account for this difference. Our data support the view that simple tests of cognitive function do not necessarily predict complete recovery from anesthesia.

No previous studies have evaluated the ability of so many potential indicators to predict movement during propofol/nitrous oxide anesthesia. In addition to determining propofol concentrations, we report EEG, pupillary, and hemodynamic data. The prediction probability ($P_k$) statistic allows us to directly compare these indicators, despite their different units of measurement. For the indicators we studied, Smith et al. have shown that, after nonlinear scaling to improve curve fit, the relative values of a logistic curve goodness-of-fit measure correlated closely with the relative values of $P_k$. An advantage of $P_k$ is that it does not require a search for nonlinear scaling. We anticipate that this technique will have numerous applications in anesthesia research.

In summary, we conclude that indices of pharmacodynamic effect, such as the EEG, pupillary light reflex, and systolic arterial blood pressure, predict movement as well as effect-site concentration during propofol/nitrous oxide anesthesia. Indices of pharmacodynamic effect are easier to measure and results are immediately available. These data suggest that monitoring such indicators during anesthesia may facilitate prevention of movement in nonparalyzed patients and prevention of awareness in paralyzed patients.

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