Electrophysiologic Effects of Propofol Sedation

J. Robert Sneyd, MA, MD, FRCA, Satwant K. Samra, MD, Bruce Davidson, BS, Takuzo Kishimoto, MD, PhD, Chitoshi Kadoya, MD, PhD, and Edward F. Domino, MD
Departments of Anesthesiology and Pharmacology, University of Michigan, Ann Arbor, Michigan

The intravenous anesthetic, propofol, is now widely used as a sedative for patients having surgery under local or regional anesthesia. It has been approved recently for maintaining prolonged sedation in patients in intensive care units in the United States. Its pharmacokinetic profile, associated with rapid recovery, permits repeated assessment of neurologic function in critically ill patients (closed head injury, multiple trauma, complicated vascular procedures) in whom deterioration of neurologic function is a concern. However, detailed central nervous system effects of propofol, i.e., topographic electroencephalogram (EEG) changes, effects on evoked responses, and recovery of cognitive function, have not been investigated thoroughly.

Transient $\beta$ activation of the EEG has been described in association with induction of anesthesia with propofol (1). However, the $\beta$ activity lasted only a few seconds before being superseded by $\delta$ waves. When volunteers were sedated with a fixed infusion rate of propofol ($75 \mu g \cdot kg^{-1} \cdot min^{-1}$) for 45 min, venous plasma propofol concentrations varied between 0.77 and 1.14 $\mu g/mL$ (1). This level of sedation caused sleepiness and significantly impaired cognition and recall. A sustained frontal increase in $\beta$ activity occurred during the period of sedation. The logarithm of the voltage squared (power) in the $\beta$, frequency range was the strongest predictor of recall and learning.

Anesthesiologists frequently are concerned that the use of total intravenous anesthesia, particularly if combined with skeletal muscle relaxants, may be associated with “awareness” or postoperative recall. Monitoring anesthetic “depth” is an imprecise art, at best (2). Few clinical studies (1,3-5) have attempted to identify electrophysiologic correlates of awareness, spontaneous motor movements, and/or recall using conscious sedation in volunteer subjects as a model. The results of these investigations are controversial. The amplitude of the P300 wave of the long latency auditory-evoked response (AER), or cognitive response, approached zero when end-tidal $N_2O$ reached 62% in volunteers sedated with step-wise increasing doses of nitrous oxide (3). Three of the six subjects in that investigation had a detectable P300 wave when they made no motor response to the auditory tones. The authors concluded that this represented residual cortical processing and suggested that the P300 response may be a marker of conscious awareness, with or without recall. In a separate study (4), volunteers were sedated with doses of lorazepam (which produced amnesia), secobarbital (which did not), or placebo. Lorazepam reduced the amplitude and
increased the latency of the P300 response. However, the effect of lorazepam was not significantly different from that of secobarbital. The investigators concluded that “changes in the P300 may be associated with sedation only and cannot be used as electrophysiologic predictors of amnesia.”

The purpose of the present study was: 1) to define the dose response relationships and spatial distribution of cortical \( \beta \) increases during propofol sedation; 2) to examine the relationship between the increase in \( \beta \) activity and the loss of the P300 cognitive AER since both have been claimed to be markers of recall in a previous study (3); and 3) to measure reaction time to the rare tone during propofol infusion in all subjects as a measure of sedative effect. Plasma propofol levels were measured to ascertain a “steady state” of sedation during duplicate recordings of EEG and P300-evoked responses.

Methods

Institutional approval of the protocol was obtained for this study. Ten consenting, paid, normal volunteers were recruited by local advertisement. All were in good health and of ASA physical status I. Subjects abstained from caffeine and alcohol for 24 h, and did not eat for 6 h prior to the propofol infusion. After attachment of the EEG and electrocardiogram electrodes, subjects rested in the supine position for placement of venous cannulae and subsequently for the duration of the study and recovery.

The study design is shown in Figure 1. After satisfactory baseline recordings of the EEG, P300, and reaction times had been obtained, the STANPUMP system (see below) was used to maintain four consecutive plateau plasma concentrations of propofol targeted at 0.3, 0.6, 0.9, and 1.2 \( \mu g/mL \), respectively. At each plateau, a venous sample was drawn from a large vein at the wrist after 5 min, the EEG was recorded for 2 min, two P300 AER (each consisting of 150 averaged responses) with reaction times were measured, the EEG recorded again, and a second venous sample was drawn before increasing the target plasma propofol concentration to the next plateau. Two blood samples were drawn 10 min apart. After all measurements and blood samples had been obtained at the highest plateau, the infusion was discontinued and the subject allowed to recover. A further set of EEG and P300 measurements were made when the subject appeared to be alert and reasonably well recovered from sedation (15–60 min after the infusion had been discontinued).

Propofol was infused into a forearm vein by a Harvard 22 electronic syringe pump (Harvard Apparatus, S. Natick, MA) driven by a RS232 link from an IBM compatible computer notebook (Everex Tempor LX, technical support by PBM, Pittsford, NY). The pump was controlled by the STANPUMP pharmacokinetic software model and control system (Version 10, June 1992). The STANPUMP system and its performance have been described elsewhere (6). STANPUMP is freely available from its authors through the kindness of Dr. S. L. Shafer (Anesthesiology Service (112A), PAVAMC, Palo Alto, CA). Briefly, the system used a three-compartment kinetic model, corrected for weight and age, to predict plasma and “effect site” concentrations of propofol and adjust the rate of infusion to maintain a preset predicted plasma or effect site concentration.

A second intravenous cannula was placed in a large vein on the arm opposite that used for the propofol infusion. Samples of venous blood were withdrawn 5 min after the STANPUMP apparatus had achieved the predicted plateau of plasma propofol concentration. A second sample was drawn 10 min later, at the end of all measurements on a particular plateau. Two further recordings were made at 15 and 30 min after the infusion was discontinued. Care was taken to clear the dead space of the cannula and the sampling line with a separate syringe before the designated sample for assay was removed; after sampling, the line was flushed with a heparinized 0.9% NaCl solution. Blood samples were transferred into a heparinized glass tube.

![Figure 1. Scheme of target plasma propofol concentration (interrupted line), actual mean plasma propofol concentration (solid line), and blood samples (arrows). The electroencephalogram recordings and P300 auditory evoked responses with reaction time measurements were taken just before and just after the two blood samples (indicated by arrows).](image-url)
and immediately centrifuged for plasma separation. Plasma samples were stored on ice for a maximum of 2 h prior to freezing to −20°C. Subsequently, plasma propofol concentration was measured by high-performance liquid chromatography with fluorescence detection using the method of Plummer (7).

The EEG was recorded using a Grass 8-28D electroencephalograph (Grass Instrument Company, Quincy, MA). EEG was recorded on 16 channels Fz, F3, T3, T4, Fp1, Fp2, C3, C4, P3, P4, O1, and O2 based on the International 10/20 System. A1–A2 were used as the monopolar reference lead. Electrocardiogram (lead II) was recorded on channel 17. An electrode cap (Electrode Cap International, Eaton, OH) was used and electrode impedances were always below 10 kΩ and usually below 5 kΩ. Filter settings were 1 and 35 Hz with the 60 Hz notch filter “on”. Subjects were given specific instructions to keep their eyes closed and motionless during the EEG recordings.

Paper recordings were kept, and a simultaneous digitized electronic record made using the software package RHYTHM 7.1 (Stellate Systems, Westmount, MA). EEG was recorded on 16 channels Fz, T3, T4, Fp1, P3, C3, P4, O1, and O2 based on the International 10/20 Electrode System. A1–A2 were used as the monopolar reference lead. Electrocardiogram (lead II) was recorded on channel 17. An electrode cap (Electrode Cap International, Eaton, OH) was used and electrode impedances were always below 10 kΩ and usually below 5 kΩ. Filter settings were 1 and 35 Hz with the 60 Hz notch filter “on”. Subjects were given specific instructions to keep their eyes closed and motionless during the EEG recordings.

Paper recordings were kept, and a simultaneous digitized electronic record made using the software package RHYTHM 7.1 (Stellate Systems, Westmount, Quebec, Canada) running on a Zenith 386/25 IBM compatible personal computer. This system has been described and validated elsewhere (8). Each 2-min recording of EEG was visually inspected at 4-s epochs and segments of EEG containing motion or other obvious artifacts were rejected. The remaining, relatively artifact-free EEG was analyzed by fast Fourier transformation (FFT) and amplitude spectra derived for each of the 16 leads recorded. The analog/digital (A/D) conversion rate was 250 Hz, and the total epoch size varied from 20 to 60 s. Frequency bands were defined as follows: δ 1–3.75 Hz, θ 4–7.5 Hz, α1 7.75–10 Hz, α2 10.25–12.5 Hz, β1 12.75–20 Hz, and β2 20.25–30 Hz. FFTs were prepared for all EEG recordings.

Within the RHYTHM 7.1 software package voltage amplitudes are represented as machine units proportional to the actual voltage. For statistical analysis and the preparation of topographic maps, the area under the amplitude-frequency plot (area under the curve) within the limits of each frequency band was computed. This area has the units µV Hz (amplitude multiplied by frequency). After FFT, the area under the curve data (as µV Hz) were first averaged across subjects at a given target concentration. Subsequently, the data within a plasma concentration were averaged across subjects for the first and second sets of data at each plateau propofol concentration.

The data from all 16 channels were averaged together in order to describe the gross EEG effects by frequency band. The average amplitude for each band (in units proportional to µV) was obtained by dividing the area under the amplitude-frequency plot by the width of the frequency band (number of 0.25 Hz bins in that band). Similar divisions were performed for the other bands according to their band width.

Topographic maps were prepared using the RHYTHM 7.1 software and printed on a Hewlett-Packard Paintjet color graphic printer (Model 3630A). A four nearest-neighbor algorithm was used in the interpolation; for each point of the picture the four nearest electrodes were determined. The interpolated value was then taken as the average of the distance weighed values of these four. Each weight was inversely proportional to the cube of the distance.

The stimulation and recording variables for recording P300 AER follows: Site = right or left ear with acoustically shielded earphones; Tones = frequency of 750 Hz for frequent tones and 2000 Hz for rare tones. Ratio of frequent to rare tones, 80:20; Rate = 0.8/s; Intensity = 70 dB; Sweep time = 800 ms; Electrode placement* = both ear lobes and vertex (Cz); Electrode impedance = <5 kΩ; Filters = 1–30 Hz; Repetitions per recording = two series of 150 tones at each plateau propofol concentration. (*Position designated by the International 10–20 Electrode System.)

They were recorded using the Compact Four electrodiagnostic system (Nicolet Biomedical Instruments, Madison, WI). Software version H3 was used. All subjects could hear the tones well in both ears. Amplitude and latency of the N1, P300, and N2 waves were measured using the cursor system of the Compact Four. Two consecutive AER measurements were made between two 2-min EEG recordings.

Reaction times were measured and correct responses identified using a custom made software instrument written within the package LABVIEW version 2.2.1 (National Instruments Corporation, Austin, TX). Briefly, the tones generated by the Compact Four triggered a timing and analysis algorithm. Timing and data acquisition were accomplished within a NB-MIO-16L multifunction input/output board and a NB-DMAC-8-G direct memory access board (both from the National Instruments Corporation) mounted in an Apple Macintosh IIfx computer with 20 megabytes of random access memory. The subject held a thumb-operated switch and was instructed to press it in response to each “rare” tone. When the tone was acquired, the program determined its frequency and whether the subject responded. The interval between the start of the rare tone and the closure of the switch was timed and recorded to 0.1 ms.

Data were analyzed using Statview DE + Graphics V1.04 (Abacus Concepts, Berkeley, CA). Descriptive statistics were derived for the demographic data. Comparisons between different treatment conditions were made using a one-way analysis of variance for repeated measure with P < 0.05 as the levels of significance using the Scheffe's F-test.
Table 1. Demographic Characteristics of the Volunteers

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CI = confidence interval.

Results

Demographic data, propofol dosage, and the duration of sedation are shown in Table 1. The duration of each individual plateau was determined by the need to obtain satisfactory electrophysiologic recordings. An uncomplicated plateau lasted 19–23 min. Those subjects in whom the recording time was prolonged received a greater dose of propofol per kilogram than those in whom recordings were made without difficulty. All of the subjects completed the study and none were completely unresponsive to the P300 rare tones at any of the four plasma propofol concentrations.

Target and measured plasma propofol concentrations are shown in Figure 1. The measured mean ± se plasma propofol concentrations were 0.152 ± 0.042, 0.372 ± 0.078, 0.679 ± 0.104, and 1.065 ± 0.112 which were slightly lower than the target concentrations. The difference between the target and measured plasma propofol concentrations was greatest at the lowest target concentration and smallest at the highest target concentration. The concentrations during the electrophysiologic measurements were between those measured at the 5-min point and the end of each plateau. It should be noted that there was a trend for a greater increase in plasma propofol at the end than at the beginning of the infusion step, suggesting better equilibration between the arterial and venous blood concentrations toward the end of each plateau. However, there were no statistically significant differences in the mean plasma concentrations at each plateau so the data were pooled as a mean of means.

The rare and frequent AER from a representative subject are shown in Figure 2. Sedation at a mean plasma propofol concentration of 1.065 µg/mL attenuated the amplitude of P300 in all subjects. It did not return to its baseline appearance until well after the subjects appeared to be recovered from the sedation. Recovery of P300 amplitude was much slower than clinical recovery from sedation. The longest recovery time was 60 min after the end of propofol infusion. Several of our subjects continued to respond to the rare tones at a time when the P300 AER could not be detected. Unfortunately, we are unable to provide quantitative data on changes in amplitude and recovery time of P300 in all subjects because data from Subjects 1–7 were erased accidentally before measurements were made. Figure 3 shows the changes observed in three subjects plotted for the entire group mean propofol concentrations.

Propofol caused a dose-related increase in reaction time and a corresponding reduction in accuracy (Figures 4 and 5). Reaction times were significantly prolonged at the 0.679- and 1.065-µg/mL plateaus. The percentage of correct responses was significantly reduced at the 1.065-µg/mL plateau (analysis of variance, Scheffe's F-test, P < 0.05). At all venous concentrations of propofol, mean reaction times were increased although this increase was only statistically significant at the higher plasma concentrations.

Changes in EEG amplitude for the six frequency bands studied are shown in Figure 6. There was no significant increase in β activity of the EEG at plasma propofol concentrations of 0.152 and 0.372 µg/mL. At the higher concentrations of 0.679 and 1.065 µg/mL, β1 activity was significantly increased (P < 0.05 analysis of variance, Scheffe's F-test). δ and β2 activity were also increased at these target concentrations, but the increase did not achieve statistical significance. The increase in β1 and β2 activity was reversed when sedation was discontinued. The spatial distribution of the β1 increase was frontal and central with relative sparing of the temporal lobes (Figure 7).

Discussion

All of the subjects demonstrated a dose-related depression of all of the indices measured which correlated with the venous concentrations of propofol. None of the subjects wereunarousable during the study, although some fell asleep at the highest plasma concentration.
Figure 3. The effect of propofol sedation on the auditory evoked response in Subjects 8, 9, and 10. In Subject 10 (△) the P300 wave was present in the first measurement made at a target plasma propofol concentration of 1.2 µg/ml but not in the second. □ Subject 8; ● Subject 9.

Figure 4. The effect of propofol sedation on reaction time. Note that the reaction time was significantly increased with the larger plasma propofol concentrations. Significant change from the control condition, P < 0.05 analysis of variance, Scheffe’s F test.

propofol concentration. Most subjects appeared entirely normal at the two lower plasma propofol concentrations. It is well known that arterial and venous plasma concentrations of propofol may vary considerably. We chose to measure venous (instead of arterial) propofol levels because of lower morbidity and better acceptability by both the Institutional Review Board and the volunteer subjects. The purpose of measuring blood levels in this investigation was to assure a steady-state sedation level during the period of EEG recording. The data obtained (Figure 1) showed that, although not perfect, a reasonable steady-state plasma concentration was achieved. The disparity between the target and measured plasma propofol concentrations is not unexpected. The STANPUMP system uses a pharmacokinetic model to predict plasma propofol concentrations when arterial and venous concentrations are in equilibrium. The rate constants within this model are based on measurements of plasma propofol concentration in patients who had received full anesthetic doses of propofol. The most likely explanation for the observed differences is that during sedation, hepatic blood flow and propofol clearance are greater than during anesthesia (i.e., with increasing propofol concentrations). An alternative explanation is that the plasma samples deteriorated during storage. However, this is unlikely based on the way the blood samples were handled and stored.

The present experimental protocol was designed to provide progressively increasing blood (and brain) propofol concentrations. While this approach has some statistical limitations, carryover effects are minimized by following lower concentrations with higher ones. An alternative scheme with a randomized sequence of concentrations was considered but rejected, inasmuch as this would complicate analysis and interpretation. Further, to have a scheme in which higher concentrations were sometimes followed by lower ones would have caused an unacceptable prolongation of the study, as delays would have been needed to allow plasma propofol concentrations to decrease to the desired lower level.

Figure 5. The effect of propofol sedation on the percentage of correct responses to the P300 “rare” tone. Reaction time was significantly increased at the larger plasma propofol concentrations. Significant change from the control condition, P < 0.05 analysis of variance, Scheffe’s F test.
The finding of $\beta$ activation of the EEG at the two higher concentrations of propofol confirms that of Veselis et al. (1) who observed similar changes at approximately the same plasma propofol concentrations. They found that $\beta$ activation was greatest in leads $F_7$ and $C_7$, but were unable to further define the spatial distribution, as they only studied the four leads $F_7$, $C_7$, $P_7$, and $O_7$. The present study provides additional data of a cortical brain topographic map projected to a planar surface based upon 16 channels of EEG recordings.

Increases in frontal $\beta$ activity have been described in association with benzodiazepines and barbiturates (9,10). The mechanism of action of these hypnotics is due to their affinity for the $\gamma$-aminobutyric acid A (GABA$_A$) chloride receptor complex which is believed to enhance GABA effects and thus produce sedation (11,12). It appears that selective increases in $\beta$ EEG activity are correlated with these effects. A selective increase in $\beta_1$ EEG activity in this study was associated with central nervous system depression and not stimulation. The former would be expected of drugs which enhance brain GABA activity at a postsynaptic neuronal level.

In a study of the EEG effects of propofol during induction, maintenance, and recovery from anesthesia, Herregods et al. (13) concluded that “the appearance of beta waves in the EEG or a zero crossing frequency greater than 10 Hz indicated pending arousal.” In the present study, the appearance of an increase in $\beta$ activity coincided with prolongation of reaction times, a reduction in response rates, and a disappearance of the P300 AER response. The observations by Herregods et al. (13) and those described in this report are totally consistent as viewing the same phenomenon from either recovery from anesthesia or induction of sedation.

The ability of some of the subjects to continue to respond correctly to the auditory rare tones after their P300 AER had disappeared calls into question whether the P300 can be described as an index of conscious awareness with or without recall if, in its absence, individuals were able to respond to the rare tones. Presumably, it is not possible to respond correctly to the rare tones without some degree of conscious awareness. It is most unlikely that loss of the P300 could be explained by technical failure because the subjects had satisfactory electrode impedances and the P300 did reappear during the recovery phase of the study. A further conundrum is the slow recovery of P300 in subjects who by other criteria were fully recovered from sedation. This delay in recovery of the P300 response was also noted by Jessop et al. (3) who found that the P300 amplitude had returned to control values in only one of their six subjects 15-20 min after the cessation of N$_2$O inhalation. It appears possible to have no P300 responses in subjects who are still able to respond and, conversely, to have a markedly attenuated P300 in subjects who are otherwise awake, aware, and clinically recovered from sedation. In light of these findings, the sensitivity and specificity of P300 as an index of conscious awareness must be questioned. Our data agree with a previous investigation (4) that the P300 is markedly attenuated with sedation and cannot be used as a marker of awareness.

Unfortunately, no quantitative data on recall were obtained in the present study. All of the subjects were maintained in a conscious sedated state. During anesthesia, transition from consciousness through conscious awareness without recall to unconsciousness appears to be closely associated with some of these EEG changes, but further research is needed. At present, no single marker is sufficiently reliable to distinguish between those patients who are and those...
who are not at risk from perioperative awareness. The plasma propofol concentrations that were measured were lower than those targeted. Nevertheless, the venous concentrations of propofol achieved in this study were sufficient to effectively sedate all of the subjects studied and to maintain a clinically desirable level of conscious sedation suitable for some perioperative procedures.

References


