Topographic electroencephalogram of propofol-induced conscious sedation

Objectives: To determine the effects of increasing doses of propofol that induce conscious sedation on the topographic electroencephalogram (EEG) of human volunteers and to test the hypothesis that more frontal brain areas are affected by low doses of propofol.
Methods: The scalp EEG was recorded monopolarly from 16 different sites based on the 10-20 International System. Microcomputer-based hardware and RHYTHM 7.1 software were used to obtain quantitative power frequency topographic EEG data. A total of 10 normal adult volunteers were given incremental doses of propofol targeted to plasma concentrations of 0 to 1200 ng/ml.
Results: Sedative concentrations of propofol produced a dramatic increase in $beta_1$, an increase in $alpha_2$ and $beta_2$, and an increase in delta activity at the largest concentration, with almost no change in theta activity. The increase in $beta_1$ activity had a linear correlation with plasma propofol levels ($r = 0.9$). Topographic mapping indicated that $beta_1$ activation was primarily in the frontal and central regions, with focal changes more in the left hemisphere.
Conclusions: Topographic brain EEG mapping techniques indicate that frontal brain $beta_1$ EEG activity may be useful as an objective brain index of propofol conscious sedation. (CLIN PHARMACOL THER 1995;58:666-74.)

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This study describes the actions of increasing sedative doses of propofol on the topographic electroencephalogram (EEG) with use of power-frequency spectral analysis. It is preceded by a complementary report that covers additional clinical pharmacologic findings.[1,2] The research question to be answered was whether multichannel EEG recordings would reveal that frontal brain areas are more affected during propofol-induced conscious sedation in humans, and whether there is a correlation with plasma propofol levels. If there is a correlation, what is the mean effective plasma concentration (EC_{50}) for the EEG changes observed? The results of this study indicate that frontal and central brain cortical areas are more responsive to low doses of propofol in humans and may be useful for monitoring the sedation status of patients.

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METHODS

Subjects. This study was approved by the Committee to Review Clinical Research and Investigation Involving Human Beings (University of Michigan Medical School, Ann Arbor, Mich.). Ten healthy, drug-free, paid adult volunteers (seven men and three women; age (mean ± SEM), 25.4 ± 3.3 years; weight, 74.9 ±

5.0 kg) were recruited by local advertisement. All subjects were in good health (American Society of Anesthesiologists physical status class I). Nine subjects were right-handed and one was born with left-hand dominance and forced to convert to right-hand preferred usage. All subjects gave written informed consent. Each subject abstained from caffeine, alcohol, and nicotine on the day of the study and was asked to abstain from eating or drinking for 6 hours beforehand. They were also asked not to use any psychoactive drugs for several weeks before the study. No urine tests were performed to confirm compliance, but the subjects assured us that they did comply. After attachment of the scalp EEG and electrocardiogram (ECG; lead II) electrodes, each subject rested in the supine position for placement of venous cannulas and was asked to relax with his or her eyes closed for the duration of the study and during subsequent partial recovery. The subjects did not go to sleep.

Topographic EEG recordings. Details of the EEG techniques used are described elsewhere.[2,3] In brief, a total of 16 cortical recording sites were used for monopolar recordings linked to A_1-A_2 as the reference lead per the 10-20 International System.[4] An electrode cap (Electrode Cap International, Eaton, Ohio) was placed on the subject's head with Grass electrode paste (Astro-Med, Inc., West Warwick, R.I.) applied to each electrode. Electrode impedances were always below 10 kΩ and usually below 5 kΩ. The EEG records taken from F_7, F_8, T_3, T_4, T_5, T_6, F_{p1}, F_{p2}, F_3, F_4, C_3, C_4, P_3, P_4, O_1, and O_2 were recorded on channels 1 to 16 of a Grass electroencephalograph model 8-24D (Astro-Med, Inc.). The ECG was recorded on channel 17. Filter settings were 60 Hz for notch filter, on; 1 Hz for high-pass filter; and 35 Hz for low-pass filter. Paper recordings were kept and simultaneous computerized records were made with use of the software package RHYTHM 7.1 (Stellate Systems, Westmount, Quebec, Canada) on a personal computer (Zenith 386/25, Zenith Data Systems, Denver, Colo.). Frequency bands were defined as follows: delta, 1 to 3.75 Hz; theta, 4 to 7.5 Hz; $alpha_1$, 7.75 to 10 Hz; $alpha_2$, 10.25 to 12.5 Hz; $beta_1$, 12.75 to 20 Hz; and $beta_2$, 20.25 to 30 Hz.

Data analysis. Computer analysis of the electrophysiologic data was completed offline by the software package RHYTHM 7.1 on a Zenith computer. To reject EEG artifacts, each 2-minute recording of the EEG was carefully inspected and segments of EEG free from obvious artifacts were accepted in blocks of 2 seconds. As many artifact-free segments as possible were collected and submitted to the quantitative analysis. This included most of the EEG data, including all of the variability normally observed with resting, eyes-closed recordings. The subjects did not go to sleep, so there was no confounding of the EEG data between conscious sedation and stages of sleep. The EEG was digitalized at a sampling rate of every $1/128$ second and subjected to fast Fourier transformation (FFT) into 0.25 Hz bins, creating power spectra up to 30 Hz, including delta through $beta_2$ bands for each monopolar scalp recording. Further, the area under the power-frequency plot within a boundary of each frequency band (as the power integrated over each frequency band) was also computed for each lead. This value is proportional to the mean multiplied by the band width and was adopted to represent the EEG activity of each respective frequency band.

The data from all 16 channels were averaged for each epoch to describe the gross effects of propofol on EEG total power for each frequency band. The data for each individual subject were normalized and then averaged across the subjects at each experimental condition. Significance of the data was evaluated with use of the Student paired *t* test.

To describe the difference in EEG activity between the left and right hemispheres after propofol infusion, $beta_1$ activities at each experimental condition were computed for each individual scalp lead and then averaged for 10 subjects. Further, the increase in $beta_1$ activity from the control level was also calculated for each individual scalp lead and averaged for 10 subjects at each condition.

Topographic maps, which show the spatial distribution of the power integrated over each frequency band, were created by transforming the EEG activity into color gradients on respective cortical brain regions with use of RHYTHM 7.1 software. A four nearest-neighbor algorithm (quadratic interpolation) is used in RHYTHM 7.1 software to compute interpolation. The topographic mappings were printed with a Hewlett-Packard PaintJet color graphic printer (model 3630A; Hewlett-Packard Co., San Diego, Calif.).

The EEG values, as a function of plasma propofol concentrations, were fitted (when possible) to logistic data with use of the InPlot computer package (GraphPad, San Diego, Calif.).

Experimental design. After satisfactory recording of the control EEG for at least 3 minutes, an intravenous infusion of propofol was given by means of a computerized infusion system. Four plateau plasma concentrations of propofol (0.3, 0.6, 0.9, and 1.2 mg/ml), each lasting 20 minutes, were targeted to be infused by this system. At each plateau, EEGs were recorded at 5 and 15 minutes after the start of the in-

fusion for 2 minutes for each recording. Blood samples were taken immediately before the first EEG recording and then approximately 5 and 20 minutes after each step of the propofol infusion. A total of nine blood samples were drawn from each patient. After all EEG recordings and blood samples had been obtained at the highest concentration, the infusion was discontinued, and the subject was allowed to recover. In the course of the recovery, EEGs were recorded for 2 minutes at about 5 or 30 minutes, or more, after cessation of infusion.

Propofol in a standard emulsion formulation (1% in soybean oil, 100 mg/ml; 22.5 mg/ml glycerol; 12 mg/ml purified egg lecithin with sodium hydroxide and sterile water adjusted to pH 7.0 to 8.5) was infused into a forearm vein by a Harvard 22 electronic syringe pump (Harvard Apparatus Inc., South Natick, Mass.). The pump was controlled by a STANPUMP* pharmacokinetic software and control system (Version 10, June 1992) targeted for steady-state plasma concentrations. In brief, the system uses a three-compartment kinetic model, corrected for weight and age, to predict plasma and "effect-site" concentrations of propofol. It adjusts the rate of infusion to maintain a preset predicted plasma or effect-site concentration. The STANPUMP system and its performance have already been described.[5]

A second intravenous cannula was placed in an antecubital vein of the forearm opposite that used for the propofol infusion. Two samples of venous blood were taken at each targeted plateau concentration. The first was sampled 5 minutes after the beginning of each step of the computerized infusion, and the second was sampled at the end of the second EEG recording for each step. Care was taken to clear the dead space of the cannula, and the sampling line was flushed with a heparinized 0.9% sodium chloride solution. Blood samples were transferred into a heparinized glass tube and immediately centrifuged for plasma separation. Plasma samples were stored on ice for a maximum of 2 hours before freezing to −20° C. Subsequently, each plasma propofol concentration was assayed.[6] Any remaining propofol in the original stock ampule, infusion lines, and pump syringe was discarded to prevent bacterial growth and cross-volunteer contamination.

RESULTS

Global change from control: Incremental increases in plasma propofol concentrations. The experimental design required 20-minute steps of increasing plasma propofol concentrations. Because of practical experimental considerations, the actual mean duration of individual uncomplicated steps ranged from 19 to 23 minutes. In a complicated case, the total duration of propofol infusion, including four steps of increasing doses, was prolonged from $4 \times 20 = 80$, up to 124 minutes, to obtain satisfactory EEG recordings. Subjects for whom recording times were prolonged received larger cumulative doses of propofol, although the infusion rate was always held to the larger plasma concentration. Total doses of propofol ranged from 3.1 to 5.5 mg/kg body weight. The mean ± SEM plasma propofol levels for each incremental step 5 minutes after the start of the infusion step and at the end of the infusion step were as follows: *step 1,* 146 ± 25 and 159 ± 66; *step 2,* 331 ± 81 and 414 ± 77; *step 3,* 679 ± 148 and 697 ± 77; and *step 4,* 1039 ± 139 and 1104 ± 113 ng/ml.

Fig. 1 illustrates the concentration-effect relationship between the mean plasma concentration of propofol and EEG activity normalized to the control preinfusion for each frequency band at the end of each infusion step. The vertical axis represents the mean from 10 subjects of the total EEG power integrated over each frequency band added together across all 16 leads of the entire cortical brain area and then normalized to the control. Sedative concentrations of propofol produced a dramatic increase in total $beta_1$ activity. At a mean ± SEM concentration of 697 ± 77 ng/ml, the mean total $beta_1$ activity significantly ($p < 0.05$, paired t test) increased to 340.9% ± 82.0% of a control level. Significant increases ($p < 0.05$ and $p < 0.01$) in mean of total $beta_1$ activity were further observed at a mean ± SEM propofol concentration of 1039 ± 139 and 1140 ± 113 ng/ml. The correlation between the increase in plasma propofol and the increase in $beta_1$ activity was highly significant ($r = 0.9$, $p < 0.01$). An increase in $alpha_2$ and $beta_2$ activity and a decrease in $alpha_1$ activity were also produced with low sedative concentrations of propofol. Less marked changes were observed with an increase in total delta activity with the largest plasma concentration of propofol. There was almost no change in total theta activity.

Only the $beta_1$ EEG data (Fig. 2) could be fitted to a general logistic concentration-response curve ($r^2 = 0.997$), yielding the following values (mean ± approximate SEM):

$$\text{Maximum effect} = 663\% \pm 152\% \text{ of control}$$

$$\log_{10}(EC_{50}) = 2.913 \pm 0.117$$

*STANPUMP is freely available from its author, Dr. S. L. Shafer, Anesthesiology Service (112A), PAVAMC, 3801 Miranda Ave., Palo Alto, CA 94304.

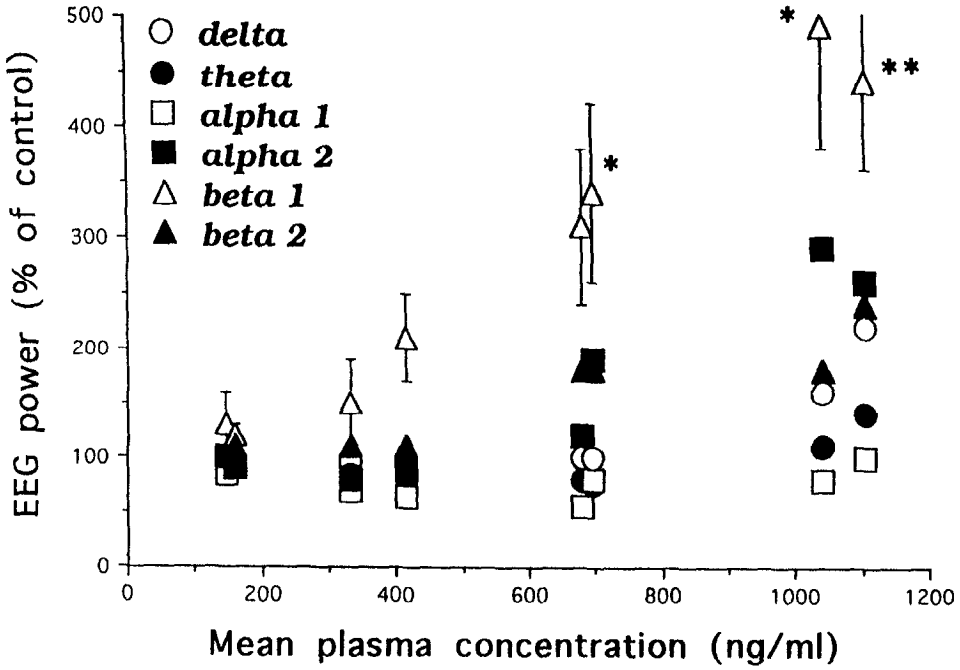

Fig. 1. Concentration-effect relationships between the mean plasma concentration of propofol and electroencephalogram (EEG) power for each frequency band. The vertical axis represents the mean of the normalized total EEG activity across all 16 leads in 10 subjects. EEG activity for each frequency band is normalized to the preinfusion control represented as the power integrated over each band and then added together across all 16 electrodes sites of the whole brain. *Vertical bars* indicate ±SEM. $*p < 0.05$; $**p < 0.01$, compared with control.

corresponding to:

EC_{50} = 818 ng/ml plasma propofol

Hill slope = 2.23 ± 0.49

The above indicated a steep concentration response curve which gives a slope that is not unusual for pharmacodynamic data.[7]

Topographic analysis: Absolute effect. Fig. 3 is a colored topographic map of the EEG for each frequency band obtained as the mean of the topographic EEG maps of all 10 subjects at each propofol concentration. During the control period, prominent $alpha_1$ and moderate $alpha_2$ activities were observed in the P_3, P_4, O_1, and O_2 regions. Moderate to low delta activity in the frontal, parietal, and occipital regions, as well as low theta activity in the parietal and occipital regions, were also observed. Consistent with previous literature in awake normal subjects, some beta activity was observed before the infusion of propofol. With a mean ± SEM plasma concentration of propofol of 159 ± 66 ng/ml, suppression of $alpha_1$ and $alpha_2$ activities were observed; no major changes were obtained in the delta, theta, or beta bands. After a mean ± SEM concentration of propofol of 414 ± 77 ng/ml, moderate activation of $beta_1$ activity was obtained in the frontal and parietal regions, whereas $beta_2$ activity was not affected. $Alpha_1$ power decreased markedly at this concentration of propofol. After a mean ± SEM concentration of propofol of 697 ± 77 ng/ml, prominent $beta_1$ activity was observed in the F_3, F_4, C_3, C_4, P_3, and P_4 regions. Delta activity was not much affected up to this concentration of propofol. $Beta_1$ activity in most leads in the left cortical hemisphere was greater than that in the right cortical hemisphere. $Beta_1$ activity in the F_{p1} region at a propofol concentration greater than 697 ± 77 ng/ml was significantly ($p < 0.05$ and $p < 0.01$) greater compared with that in F_{p2} (not shown in Fig. 3). At the highest plasma concentration of propofol (1104 ± 113 ng/ml), $beta_1$ activity further increased in the frontal and central regions, with a predominance on the left side. Increases in delta activity were seen in almost all brain areas, and moderate to high delta activity was seen in the F_3 and P_3 regions. Low to moderate $beta_2$ and $alpha_2$ activity was also seen at this concentration of propofol.

Topographic analysis: Change from baseline. Fig. 4 illustrates the mean difference (after minus before)

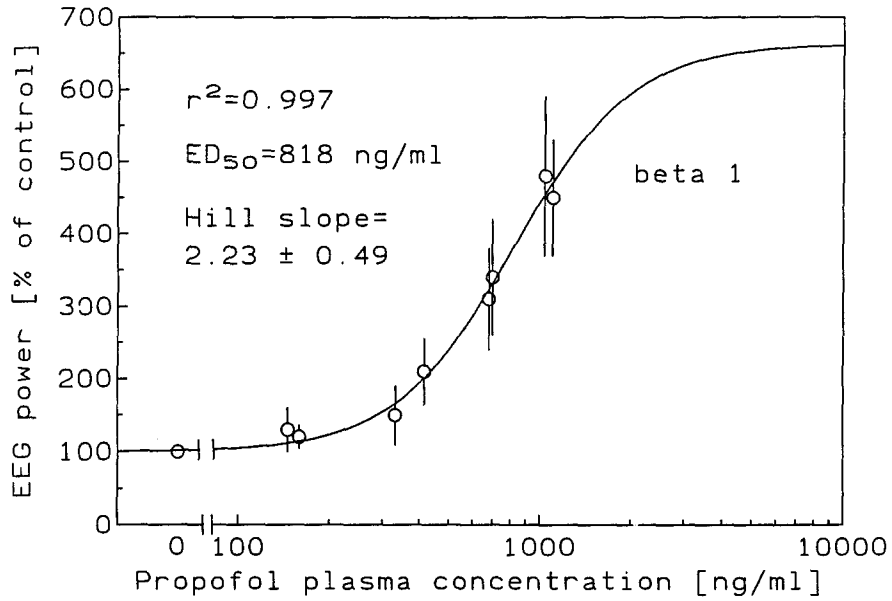

Fig. 2. Sigmoid E_{max} function plot of $beta_1$ EEG power versus venous plasma propofol concentration. Note that the data points fit the calculated curve very well as $r^2 = 0.997$. The plasma propofol concentration (EC_{50}) and Hill slope are noted.

of the topographic mapping of the EEG of all 10 subjects. This colored map shows the spatial distribution of the net increase or decrease in EEG activity from control produced by increasing concentrations of propofol. The net increase in $beta_1$ power from the control level appears to be greater in most leads from the left than the right cortical hemisphere.

Topographic analysis: Beta$_1$ power. The concentration-effect graphs in Fig. 5 show the net increase in $beta_1$ activity from the control level for each individual scalp lead. Significant ($p < 0.05$) differences between the left and right hemispheres in the increases in $beta_1$ activity were seen between F_{p1} and F_{p2} scalp sites at propofol concentrations of 1104 ± 113 ng/ml, as well as between T_3 and T_4 leads at concentrations of 697 ± 77 and 1104 ± 113 ng/ml.

DISCUSSION

The prevailing theme of this study is that venous plasma propofol concentrations may be correlated with specific regional brain EEG changes in human volunteers given doses that produce only conscious sedation. Arterial samples were not taken because of the enhanced risk and greater ease of venous punctures. This study was not concerned with the full spectrum of the EEG effects of propofol. During sedation, propofol dramatically increases $beta_1$ EEG activity. Other investigators have shown that after loss of consciousness the EEG is progressively depressed in a concentration-dependent manner, leading to burst suppression and eventually to isoelectricity. The baseline EEG data in this study, obtained during the control period before propofol, are consistent with previous findings in the literature that normal, awake, drug-free subjects with their eyes closed have predominant $alpha_1$, less $alpha_2$, and some $beta_1$ activity. After increasing small doses of propofol that produce conscious sedation (but not sleep or anesthesia), predominant occipital alpha EEG activity is reduced and $beta_1$ activity is increased, especially in the midline, frontal, and central brain areas. With the largest subanesthetic dose of propofol used in this study, delta activity was also observed more in the dominant left hemisphere.

It should be noted that the nonlinear performance of the STANPUMP algorithm in this study may be related to the fact that the algorithm was designed to use anesthetic doses of propofol and was not concerned with doses that produce only conscious sedation. Further study is needed to adapt this algorithm for sedative doses of propofol.

This study confirms previous reports[8-10] that sedative concentrations of propofol produce a dramatic increase in $beta_1$ and a decrease in alpha activity in some brain areas. The increases in EEG beta activity at similar plasma propofol concentrations are also in agreement with the literature.[11] The latter investigators reported that beta activation was greatest in scalp sites F_z and C_z, although the spatial distribution of beta activation was not clarified, inasmuch

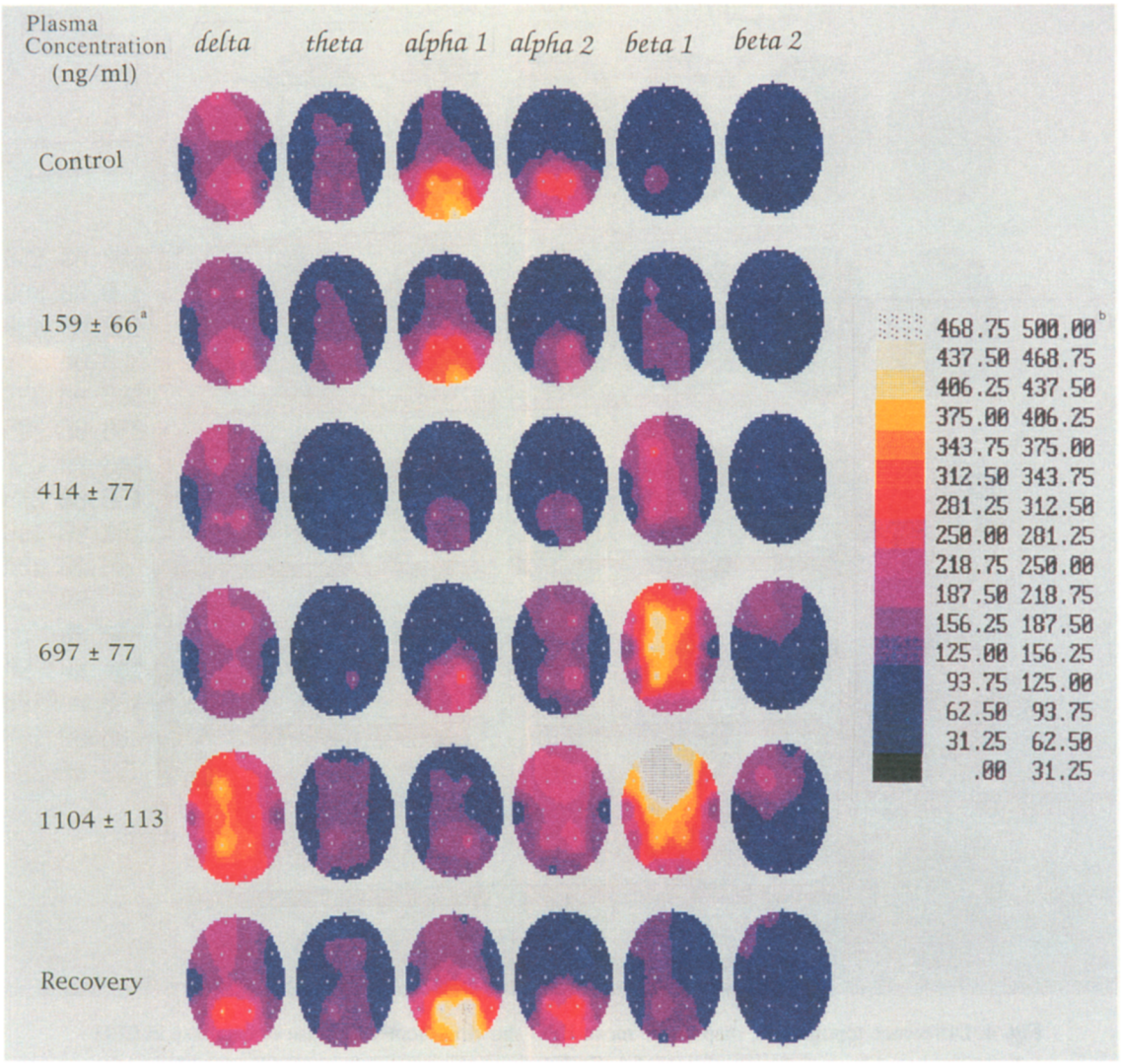

Fig. 3. Topographic mapping of the EEG for each frequency band obtained as the mean from all 10 volunteers at each plasma propofol concentration. The EEG power over each frequency band for each respective brain region was computed and represented as a color gradient with use of RHYTHM 7.1 software. A four nearest-neighbor algorithm is used in RHYTHM 7.1 software to compute interlead interpolations (quadratic interpolation). [a]Mean ± SEM plasma concentration of propofol obtained from the plasma concentrations at which the individual EEG recordings were undertaken. [b]Power integrated over each frequency band.

as only four EEG leads—F_z, C_z, P_z, and O_z—were used.

Topographically restricted EEG profiles of many different pharmacologic agents have been published.[12-19] A systematic comparison of the topographic EEG effects of different sedatives has not been undertaken. Such studies need to be done, especially with sedatives that have well-defined molecular mechanisms of action, to determine if certain topographic EEG changes are related to specific biochemical mechanisms or to the mental states of the subjects studied, irrespective of the sedative agents given.

Although there were personal and practical reasons for choosing to study propofol first, from a scientific point of view the choice was not ideal because much more information is needed on its mechanism of ac-

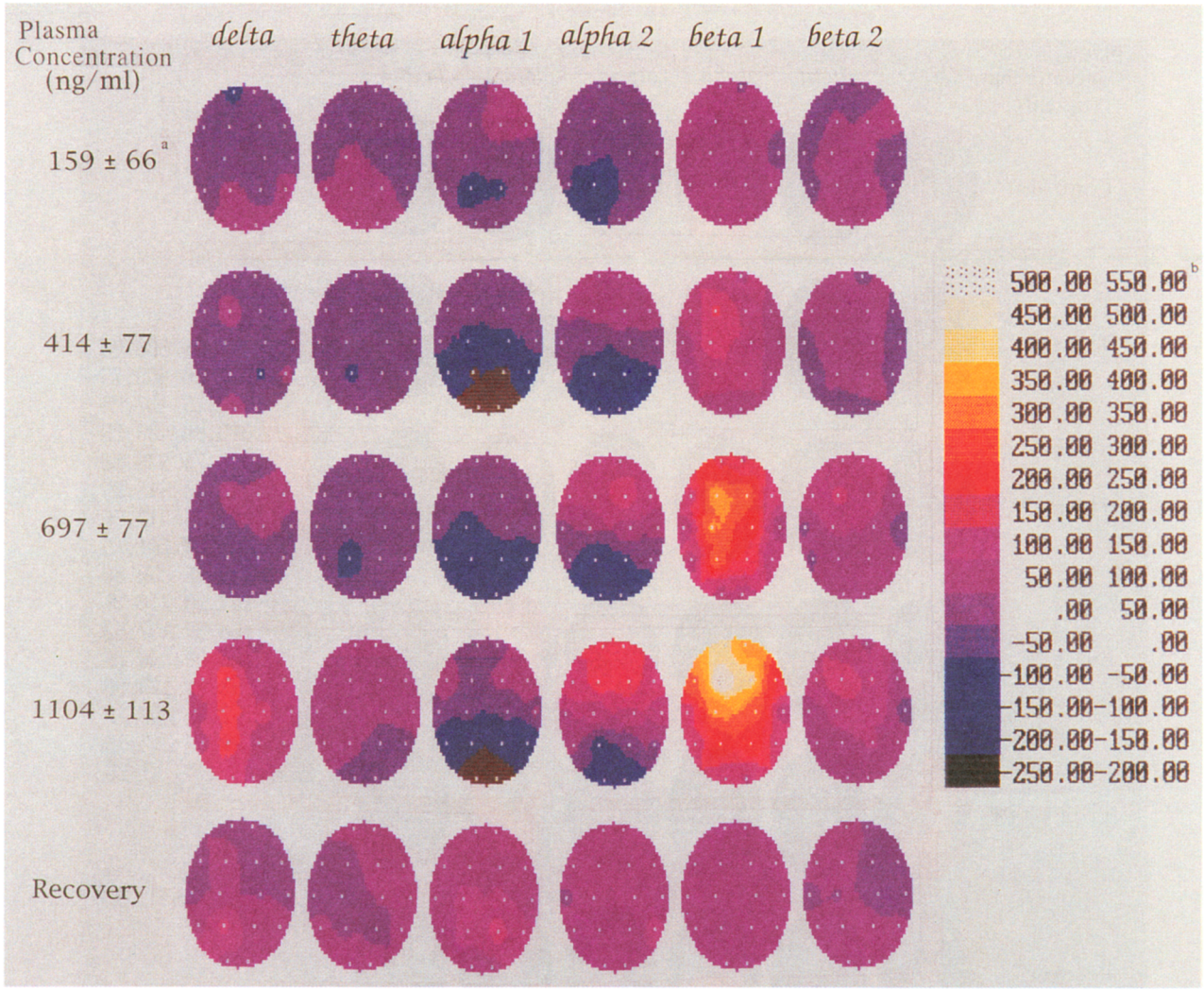

Fig. 4. Difference topographic map of the mean EEG showing the net increase or decrease in EEG activity produced by an infusion of propofol. Each topographic map was created by subtracting the mean control EEG map from the mean EEG map after each experimental condition for all 10 volunteers with use of RHYTHM 7.1 software. [a]Increase in mean plasma concentration of propofol above control. [b]Increase or decrease in total EEG power integrated over each frequency band.

tion. Recent neurochemical and electrophysiologic studies in vitro have shown that propofol does enhance the function of γ-aminobutyric acid (GABA) on $GABA_A$ receptors. However, the binding site of propofol appears to be distinct from the recognition sites for both benzodiazepines and barbiturates.[20-23] Many agents that have sedative and, in larger doses, anesthetic properties that act at the molecular level on $GABA_A$ receptors produce an increase in beta wave activity in the EEG in small doses. Frontal beta activation has been described in association with barbiturates and benzodiazepines.[17,19,24,25] However, a difference in the spatial distribution between $GABA_A$ and benzodiazepine receptors exists in human brain.[26] In addition, heterogeneity of benzodiazepine receptors is well known.[27-29] The complexity of $GABA_A$ receptors, especially their multiple allosteric binding sites, suggests that clinically important sedatives may have somewhat different sites of brain action. EEG studies in rabbits have shown that the effects of barbiturate

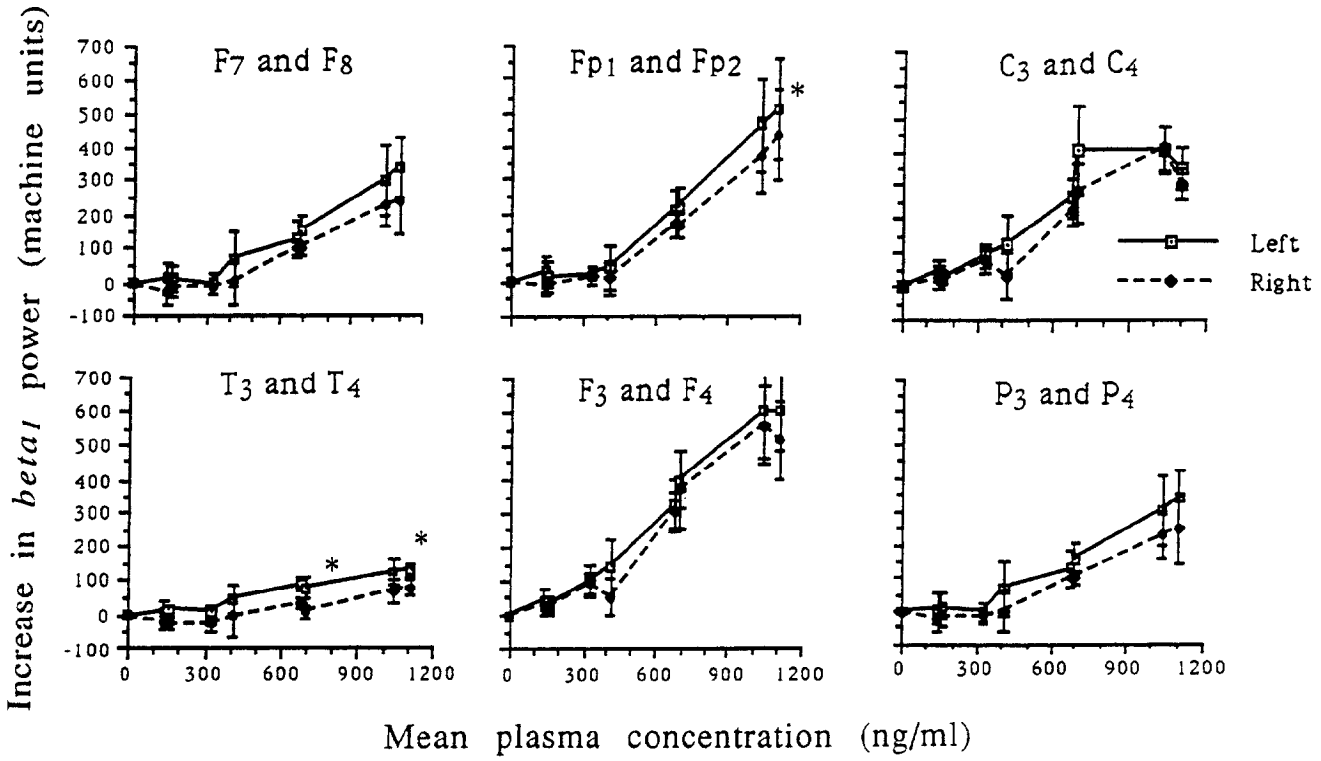

Fig. 5. Relationship between the mean plasma concentration of propofol and the net increase in $beta_1$ power from the control level obtained from F_7, F_8, T_3, T_4, F_{p1}, F_{p2}, F_3, F_4, C_3, C_4, P_3, and P_4 scalp leads. The vertical axis represents the mean increase (or decrease) in the power integrated over $beta_1$ from the control level for all 10 subjects. $*p < 0.05$, compared to the symmetrical corresponding electrode site on the scalp. Note that the left hemisphere shows a trend to slightly more $beta_1$ activity than the right hemisphere, which is also seen in Fig. 2. *Vertical bars* indicate ±SEM.

and benzodiazepine ligands can be differentiated on the basis of their EEG features.[30] In the human brain, the EEG topographic distribution of induced beta waves may vary, depending on the different cerebral distributions of their allosteric sites on $GABA_A$ receptors. Of course, surface EEG electrical events do not provide evidence of receptor distribution and mechanism of action information. Hence, one can relate EEG data only to results obtained with more specific methods. In studies of benzodiazepines, topographic maps of EEG activity obtained from the left hemisphere revealed decreases in occipital alpha and parietal delta, together with increases in posterior frontal and parietal beta activity.[18,31] In the present study, the increase in beta activity was greatest in the left dominant hemisphere, although other possibilities unrelated to hand dominance cannot be excluded.

The results of this study have implications for monitoring patients undergoing conscious sedation. Guidelines are currently being developed by the American Society of Anesthesiologists for sedation. Rather than use many EEG scalp electrodes as in this study, only a few electrodes would be needed. Technically, it would be very simple to place scalp EEG leads over the more frontal regions of the brain and use the $beta_1$ frequency band to monitor sedation levels objectively.

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