

The EEG as a Monitor of Midazolam Amnesia: Changes in Power and Topography as a Function of Amnesic State

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In order to identify EEG parameters that might be specific for identifying amnesia during midazolam infusion, we examined changes in the EEG power spectrum associated with a period of amnesia, determined by inability to recall a sequence of numbers and objects presented verbally, after intravenous midazolam 0.07 mg/kg in ten normal volunteers. Measurements were taken at baseline, during infusion immediately before and after the onset of amnesia, immediately at end of infusion, and 0.5 and 1.5 h after infusion. All subjects had onset of amnesia during infusion, were completely amnesic by the end of infusion, partially amnesic 0.5 h after infusion, and had complete recall by 1.5 h after infusion. The EEG beta power increased and alpha power decreased during amnesic periods. The beta1/alpha power ratio was the parameter most specific for amnesia. From a baseline value of 0.20 ± 0.05 (standard error of the mean [SEM]), it increased to 0.96 ± 0.26 at the end of infusion and decreased to 0.61 ± 0.15 0.5 h after infusion. By 1.5 h after infusion, all EEG parameters had returned to baseline values. Beta power changes associated with midazolam amnesia were most pronounced in the Fz and Cz lead positions, and alpha power changes were most pronounced in the Oz position. We conclude that 1) EEG power values, particularly the beta1/alpha ratio, can identify periods of amnesia after midazolam infusion; 2) specific EEG changes and the presence of amnesia vary with the probable serum concentration of midazolam; and 3) the characteristic EEG pattern during partial or complete amnesia varies as one moves across the cerebral cortex. (Key words: Anesthetics, hypnotics: midazolam. Memory: drug effects. Monitoring: electroencephalography. Sedation: intravenous.)

ONE OF THE PRINCIPAL GOALS of intravenous sedation with benzodiazepines is amnesia.¹ Midazolam, characterized by a short half-life, lack of irritation with intravenous injection, and production of amnesia, is commonly used for sedation.² Unfortunately, there are no objective monitors that can guide midazolam administration to produce

amnesia. To ensure amnesia intraoperatively, a state of excessively deep sedation is often produced.

Effects on the power spectrum of the electroencephalogram (EEG) are directly related to the serum concentrations of midazolam during light sedation. There is an increase in high-frequency EEG activity, particularly from 13–30 Hz.^{3–5} The increase in beta power is most evident over the frontal cortex, whereas there is a simultaneous decrease in the occipital alpha power.^{4,6,7} Persson *et al.* have shown that the occurrence of amnesia after midazolam administration is related to the serum concentration.⁸ It should therefore be possible to titrate midazolam to an effective amnesic dose by using changes in the EEG power spectrum. We examined the utility of EEG monitoring to detect a period of amnesia occurring when midazolam was administered to a group of volunteer subjects.

Materials and Methods

Measurements, including EEG data, were collected at the following time points: before infusion (baseline), continuously during infusion, at the end of infusion, 0.5 h after the end of infusion, and 1.5 h after the end of infusion.

SUBJECTS

Ten normal volunteers (four men and six women) aged 25–36 yr (mean 30.4 ± 3.0 yr) were studied. The protocol was approved by the local Institutional Review Board, and informed consent was obtained. Subjects were screened for medical and neurologic abnormalities and had received nothing by mouth for at least 6 h. Subjects were not allowed any caffeine on the day of the study.

INFUSION

Midazolam 0.07 mg/kg was infused intravenously at a rate of 0.5 mg/min. The period of infusion lasted approximately 10 min. At the end of infusion subjects experienced a state of light sedation in which they were drowsy but readily responsive to verbal commands.

SERUM LEVELS

Seven blood samples were obtained for midazolam assay starting at the end of the infusion for a period for 100 min. Samples were obtained either from a vein in the

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other arm, or after 20 min, from the intravenous access used for infusion. A nonlinear regression curve-fitting program (SAS software)[†] was used to fit a biexponential decay model to these data using a least-squares method. Serum values corresponding to the data acquisition points were obtained from this model.

VISUAL ANALOG SCALES

Subjective ratings of sleepiness and concentration were obtained immediately after each blood sample using a visual analog scale (VAS). Subjects indicated their current state by making a vertical mark on a 15-cm line between two labeled ends (cannot concentrate at all—can concentrate fully; very wide awake—very sleepy). The distance between the subject's mark and the low end of the scale was measured in centimeters. The four VAS measures obtained coincident with infusion and postinfusion EEG samples were compared to the baseline value with repeated-measures analysis of variance (ANOVA).

DETERMINATION OF AMNESIA

During infusion the subjects listened to a tape recording of a series of numbers (starting at 3 and increasing by intervals of 7). Subjects were told that at the end of the study they would be prompted to recall the highest number they had heard. At the end of the study, subjects reported this number and then were asked to recognize the number on a sheet that showed all of the numbers that had been presented on the tape. Since each stimulus number had been played at a constant time interval after the beginning of the tape, which was started at the beginning of infusion, the time of onset of amnesia could be established to within 30 s. Two 1-min EEG samples were chosen 30 s before and after the onset of amnesia for comparison.

In the postinfusion period, the volunteers were presented with visual and auditory stimuli for later recall. These stimuli included a person dressed in a clown costume, a person measuring the bed, and discussions with the subject about the tests being performed (*e.g.*, "Have you given blood to the Red Cross before?" or "Are you hungry now after missing breakfast?"). Note was made of any comments that the subject would initiate, such as "Boy—I really wish I were on a beach in Hawaii." The investigators would continue such conversations for a few minutes to ensure that an adequate stimulus for recall had been given. The degree of recall was defined as follows: nonamnesic = spontaneous volunteering of information or immediate recollection of exact details imme-

diately; partial amnesia = recollection with specific prompting only (*e.g.*, does not recall that he or she would rather have been in a hot climate, but does recall when Hawaii is given as a prompt); full amnesia = no recollection despite prompting.

EEG RECORDING AND ANALYSIS

EEG monitoring was accomplished with a Tracor-Northern Nomad[®] 3400 EEG monitor. Following the International 10–20 system,⁹ electrodes were placed at Fz, Cz, Pz, and Oz referenced to linked mastoids. The skin was prepared using Omni-Prep[®], and skin impedance was less than 5,000 ohms during acquisition of data. Subjects were given specific instructions not to move, talk, or open their eyes during EEG recording. The EEG analog signal was acquired using a sensitivity of $\pm 50 \mu\text{V}$; signals exceeding 99% of the full-scale deflection of $100 \mu\text{V}$ were rejected. High- and low-pass filters were set for 1 and 30 Hz respectively, and a notch filter was used to eliminate extraneous 60-Hz electrical noise. As well, during data acquisition the analog EEG waveform was examined visually for artifact. The EEG power spectrum was derived using a fast Fourier transform on 2-s epochs, and the data were stored for later analysis.

Using visual inspection of the density spectral array (DSA) display, a stable EEG pattern lasting 2–4 min was chosen for data analysis. The power spectrum was analyzed using software developed by us (RAV) and verified against the data analysis package provided by Tracor-Northern with the Nomad[®] EEG monitor. The following parameters were analyzed: the absolute power in the frequency bands delta (1–3.5 Hz), theta (4–7.5 Hz), alpha (8–13 Hz), beta1 (13.5–20 Hz), beta2 (20.5–30 Hz), and the frequencies having the 95th (spectral edge) and the 50th (median frequency) percentile of total EEG power. Power ratios including beta1/delta, alpha/delta, and beta1/alpha were analyzed. Power above and below 8 Hz also was analyzed using a high/low ratio ($\alpha + \beta 1 + \beta 2$)/($\delta + \theta$). With the exception of these ratios, absolute power data (in squared microvolts) were log-transformed before statistical analysis to achieve normality and to satisfy the assumptions of the analysis of variance.¹⁰

STATISTICAL ANALYSIS

Data from the various experimental conditions were analyzed with ANOVA using the SAS software package. A 4×4 (four conditions and four channels) repeated-measures ANOVA was performed for all EEG parameters at baseline, at the end of infusion, and 0.5 and 1.5 h post-infusion. Planned orthogonal contrasts (*a priori*, statistically independent comparisons), were computed between adjacent electrode sites and between the following data

[†]SAS Institute, Inc.: Release 6.03, 1988. SAS Circle, Box 8000, Cary NC 27512.

pairs: baseline and end of infusion, baseline and 0.5 h postinfusion, and baseline and 1.5 h postinfusion. During the infusion period, EEG samples immediately before and after the onset of amnesia were compared with a 2×4 (two conditions and four EEG channels) repeated-measures ANOVA. For the ANOVAs and contrasts, P values < 0.05 were considered significant. When indicated by the results of the multivariate ANOVA compound symmetry test, the P values reported were calculated with the more conservative Huynh-Feldt epsilon test, which is more accurate for small sample sizes. *Post hoc* comparisons were made by the paired t test between adjacent amnesic states. Using the Bonferroni correction for multiple comparisons, the critical alpha level for these *post hoc* comparisons was set at $P < 0.0016$.

Results

AMNESIC STATES

Two subjects did not have an EEG recording during partial amnesia and were dropped from further analysis.

The remaining eight subjects had onset of amnesia during the infusion of midazolam, complete amnesia at the end of infusion, and partial amnesia 0.5 h after infusion. The average length of time to the onset of amnesia after the start of infusion was 218 ± 77 (mean ± 1 standard deviation [SD]) s. At 1.5 h postinfusion, all subjects had complete recall.

EEG CHANGES ACROSS EXPERIMENTAL STATE

The changes in EEG parameters reflecting varying levels of amnesia are presented in table 1 and figures 1 to 4. Repeated-measures ANOVAs were computed for each EEG parameter comparing the end of infusion and 0.5 and 1.5 h postinfusion with baseline for the four recording sites. Significant changes across state occurred for every EEG measure except theta, total power, and the beta1/delta ratio. EEG changes were maximal between baseline and end of infusion, were still present for some variables 0.5 h postinfusion, and were no longer present 1.5 h postinfusion. Significant variations in EEG measures among

TABLE 1. Power ($\log(\mu V^2)$) and Power Ratio by EEG Lead and State

	t = 0 (B)	t = 4	t = 6	t = 10	t = 30	t = 90
BETA1						
\$*Fz	2.50 \pm 0.53	2.83 \pm 0.61	3.22 \pm 0.72	3.73 \pm 0.36	3.09 \pm 0.39	2.79 \pm 0.48
*Cz	2.70 \pm 0.55	2.99 \pm 0.58	3.31 \pm 0.61	3.75 \pm 0.30	3.22 \pm 0.40	2.95 \pm 0.47
\$*Pz	2.75 \pm 0.68	2.93 \pm 0.63	3.11 \pm 0.63	3.39 \pm 0.34	2.99 \pm 0.43	2.84 \pm 0.51
Oz	2.58 \pm 0.67	2.67 \pm 0.61	2.76 \pm 0.58	2.84 \pm 0.35	2.64 \pm 0.52	2.60 \pm 0.51
ST: 0.0003						
CH: 0.007			0.02 vs. t = 4	0.001 vs. B†	0.05 vs. B	
S*C: 0.0001					0.001 vs. t = 10	
BETA2						
\$*Fz	2.16 \pm 0.71	2.48 \pm 0.73	2.96 \pm 0.71	3.19 \pm 0.68	2.78 \pm 0.31	2.40 \pm 0.58
\$*Cz	2.43 \pm 0.70	2.73 \pm 0.68	3.17 \pm 0.60	3.28 \pm 0.52	3.01 \pm 0.40	2.63 \pm 0.57
\$*Pz	2.19 \pm 0.69	2.38 \pm 0.65	2.69 \pm 0.58	2.73 \pm 0.53	2.40 \pm 0.36	2.17 \pm 0.56
Oz	1.98 \pm 0.65	2.02 \pm 0.64	2.25 \pm 0.58	2.22 \pm 0.56	1.97 \pm 0.39	1.86 \pm 0.57
ST: 0.0004						
CH: 0.0001			0.0009 vs. t = 4	0.005 vs. B	0.06 vs. B	
S*C: 0.0001						
ALPHA						
\$*Fz	4.30 \pm 0.69	4.16 \pm 0.74	3.54 \pm 0.87	3.61 \pm 0.31	3.83 \pm 0.53	4.30 \pm 0.52
Cz	4.54 \pm 0.72	4.39 \pm 0.76	3.74 \pm 0.84	3.71 \pm 0.24	4.05 \pm 0.50	4.52 \pm 0.46
Pz	4.80 \pm 0.96	4.61 \pm 0.91	3.92 \pm 0.98	3.67 \pm 0.34	4.17 \pm 0.61	4.75 \pm 0.50
Oz	5.01 \pm 1.23	4.83 \pm 1.10	4.05 \pm 1.33	3.61 \pm 0.69	4.36 \pm 1.09	4.92 \pm 0.70
ST: 0.0019						
CH: 0.09			0.09 vs. t = 4	0.01 vs. B	0.02 vs. B	0.0002 vs. t = 30
S*C: 0.0004						
BETA1/ALPHA						
Fz	0.20 \pm 0.14	0.35 \pm 0.31	0.97 \pm 0.74	1.24 \pm 0.61	0.61 \pm 0.42	0.27 \pm 0.18
\$*Cz	0.19 \pm 0.12	0.33 \pm 0.29	0.84 \pm 0.58	1.11 \pm 0.41	0.54 \pm 0.37	0.25 \pm 0.15
\$*Pz	0.15 \pm 0.11	0.25 \pm 0.23	0.62 \pm 0.50	0.85 \pm 0.40	0.38 \pm 0.27	0.16 \pm 0.06
Oz	0.12 \pm 0.14	0.16 \pm 0.19	0.43 \pm 0.39	0.57 \pm 0.35	0.27 \pm 0.28	0.11 \pm 0.06
ST: 0.0001						
CH: 0.003			0.007 vs. t = 4	0.0005 vs. B	0.007 vs. B	0.02 vs. B
S*C: 0.006						

All values are mean ± 1 SD.

Orthogonal contrasts P value versus other state.

* Channel power different ($P < 0.05$) from adjacent channel.

\$ INFNA versus INFA.

‡ Channel power different ($P < 0.05$), t = 4 (nonamnesic) versus t

= 6 (amnesic), during infusion.

† Baseline.

ST = ANOVA P value across state; CH = ANOVA P value across channel; S*C = ANOVA P value state by channel interaction.

the four electrode sites were present for all parameters except for total power, median frequency, and the beta1/delta ratio.

Although total power did not vary across the experimental state, there were significant changes in individual EEG bands when compared to baseline. Log beta1 ($P < 0.001$) and log beta2 ($P < 0.005$) power increased during midazolam infusion; the highest values were obtained at the end of infusion (figs. 1 and 2 and table 1). The variation in log alpha power across state was also highly significant ($P < 0.002$); alpha activity was strongly decreased at the end of infusion and 0.5 h postinfusion but returned to baseline levels at 1.5 h postinfusion (see Fig 3). Log delta power increased transiently during midazolam infusion ($P < 0.003$) but was unchanged in other conditions. Spectral edge at Fz increased from 21.6 ± 4.8 Hz at baseline to 25.1 ± 4.9 Hz at the end of infusion; it remained high until 0.5 h postinfusion (25.1 ± 3.7 Hz), but only at 0.5 h postinfusion did it become statistically significant ($P < 0.03$). Although the overall change in median frequency was statistically significant ($P < 0.04$), it increased only marginally (at Fz) from a baseline value of 8.4 ± 0.8 Hz to a value of 11.0 ± 3.0 Hz by the end of infusion ($P < 0.10$) and was not able to discriminate between other time periods. At the end of infusion, the beta1/alpha ratio increased ($P < 0.0005$) (fig. 4), the alpha/delta ratio decreased ($P < 0.003$), and the high-/low-power ratio decreased ($P < 0.02$), compared with baseline. This corresponds to the peak EEG (and presumably drug) effect.

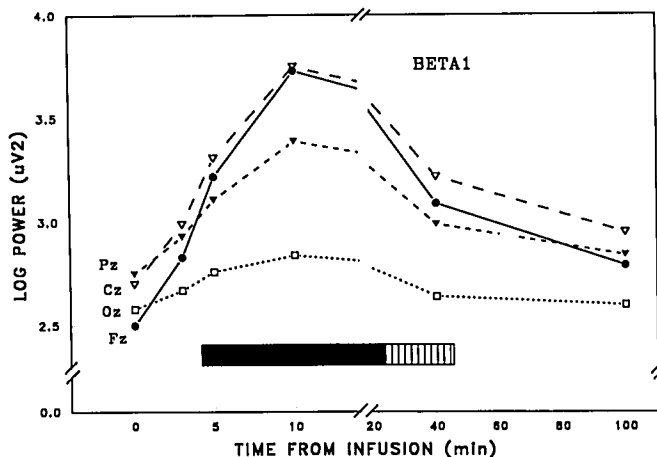


FIG. 1. Change in log beta1 power (corresponding to an EEG frequency of 13.5–20 Hz) as a function of amnesic state and electrode position. Note that beta power increases most in the frontal and central leads. In figures 1–4 electrode positions are as follows: Fz = frontal midline; Cz = central midline; Pz = parietal midline; and Oz = occipital midline. In figures 1–4 time 0 corresponds to the beginning of midazolam infusion. The filled portion of the bar above the x-axis indicates the duration of complete amnesia; the striped portion indicates the duration of partial amnesia. Error bars in figures 1–4 are ± 1 SEM.

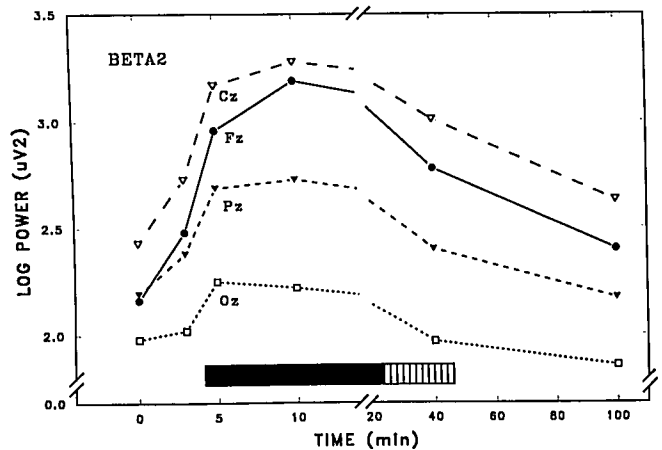


FIG. 2. Change in log beta2 power (20.5–30 Hz) as a function of amnesic state and electrode position. Beta2 power increases most in the frontal and central leads, as does beta1 power, but shows a greater change from baseline than beta1 power. (For abbreviations see legend to figure 1.)

In the comparison of adjacent states, beta1 power decreased from a period of complete amnesia at the end of infusion to partial amnesia 0.5 h postinfusion ($P < 0.001$) and had returned to baseline levels at 1.5 h postinfusion. As the state of the subjects changed from partial amnesia at 0.5 h postinfusion to complete recall at 1.5 h postinfusion, alpha power returned to baseline values ($P < 0.0002$). Changes in other EEG parameters did not meet the Bonferroni significance criterion.

EEG INDICES AT ONSET OF AMNESIA

In addition to these overall EEG changes between baseline, the end of infusion, and 0.5 and 1.5 h postinfusion, we took a closer look at the EEG characteristics of the minute immediately preceding and after the onset

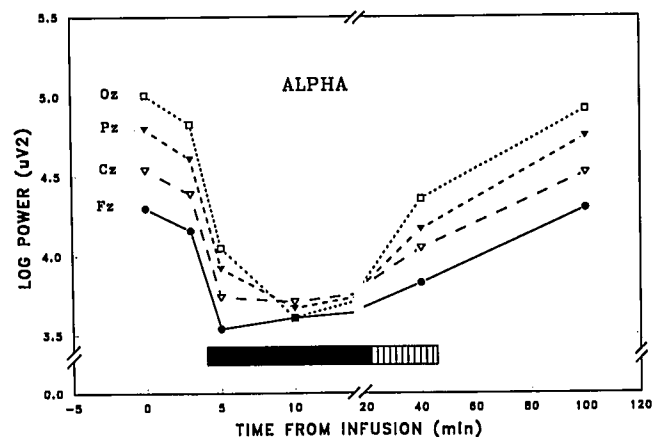


FIG. 3. Change in log alpha power (8–13 Hz) as a function of amnesic state and electrode position. The largest changes are noted in the occipital lead, where alpha power is highest during relaxation with eyes closed before drug administration. (For abbreviations see figure 1.)

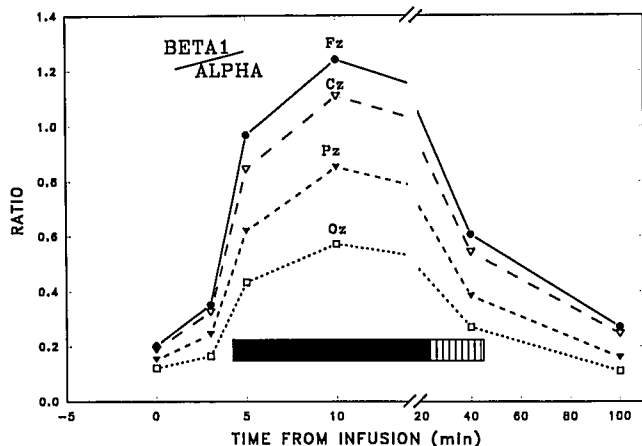


FIG. 4. Change in ratio of beta1/alpha power as a function of amnesic state and electrode position. The ratio reflects opposing effects of increasing beta and decreasing alpha power. Though of different magnitude in different leads, the change in ratio is consistent at each lead. (For abbreviations see legend to figure 1.)

of amnesia during the midazolam infusion (Table 1). Comparison between the 1-min averages from the non-amnesic period of the infusion and the amnesic period of the infusion revealed significant increases in beta1 ($P = 0.02$) and beta2 ($P < 0.001$) power and spectral edge frequency (from 21.1 ± 3.1 Hz during infusion before amnesia to 23.3 ± 2.0 Hz after onset of amnesia ($P < 0.004$) (table 1 and figs. 1 and 2). The median frequency, however, was unable to differentiate the two states. Alpha power showed a marginal decrease immediately after the onset of amnesia ($P < 0.09$). The beta1/alpha power ratio increased almost three-fold, from 0.35 ± 0.11 (SEM) to 0.96 ± 0.26 ($P < 0.007$) (figs. 4 and 5), and the alpha/delta ratio decreased ($P < 0.05$).

As can be seen from figures 4 and 5, the beta1/alpha ratio increased substantially at the onset of amnesia. The corresponding DSA displays are shown in figure 6. (Note that changes in the DSA are readily appreciated by the naked eye on the color monitor but are not as pronounced on a black and white photograph.) The primary changes seen are the loss of alpha and variable increases in beta power. These changes are more or less visible depending upon the sensitivity of the display. The changes associated with amnesic midazolam effect are more readily apparent using the beta1/alpha power ratio trend, as shown in figure 5.

During the infusion period, significant differences between adjacent electrode sites along the anterior-posterior axis were found for the spectral edge and for log absolute power in every bandwidth, although these were less marked for delta and total power. However, only for log beta2 power did these topographic differences vary between nonamnesic and amnesic periods during infusion,

with the increase in power being larger at Cz and Pz during the amnesic phase.

SERUM CONCENTRATIONS

Serum concentrations during the infusion itself were not available for analysis. At 0.5 h postinfusion, the mean blood concentration of midazolam was 49.6 ± 4.7 (SEM), whereas at 1.5 h postinfusion, the serum concentration had dropped to 22.0 ± 3.0 ng/ml.

VISUAL ANALOG SCALES

There were significant changes in the VAS for both sleepiness and concentration for the study period. With midazolam infusion, sleepiness increased from 3.3 to 8.0 ($P < 0.004$), and concentration decreased from 12.5 to 8.2 ($P < 0.006$) (fig. 7). The ANOVAs computed on the four sleepiness and concentration ratings taken concomitantly with the EEG showed significant variation over time ($P < 0.004$). The baseline values for both sleepiness and concentration differed significantly from those taken during and after the infusion but not from self-ratings taken 1.5 h postinfusion. Both measures of sedation remained relatively stable between the end of infusion and 0.5 h after infusion, despite pronounced changes in the EEG and presumably declining midazolam serum levels.

The VAS ratings of sleepiness and concentration were highly correlated. Using Fisher's *r*-to-*z* transform, mean correlations between the two VAS ranged from -0.76 for the three baseline ratings, to -0.86 for the two in-

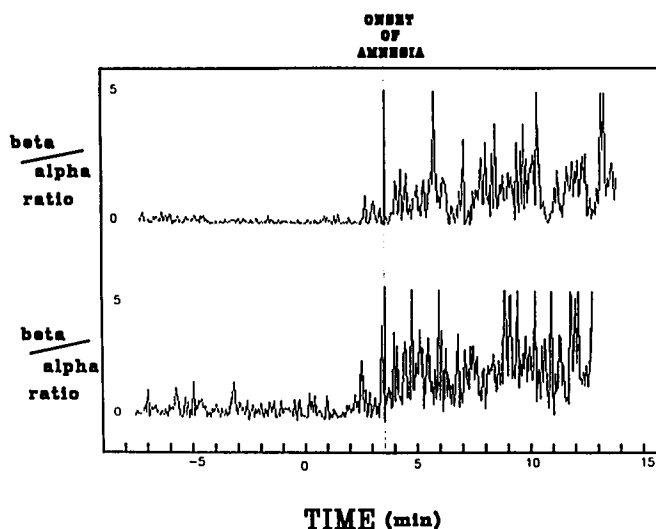
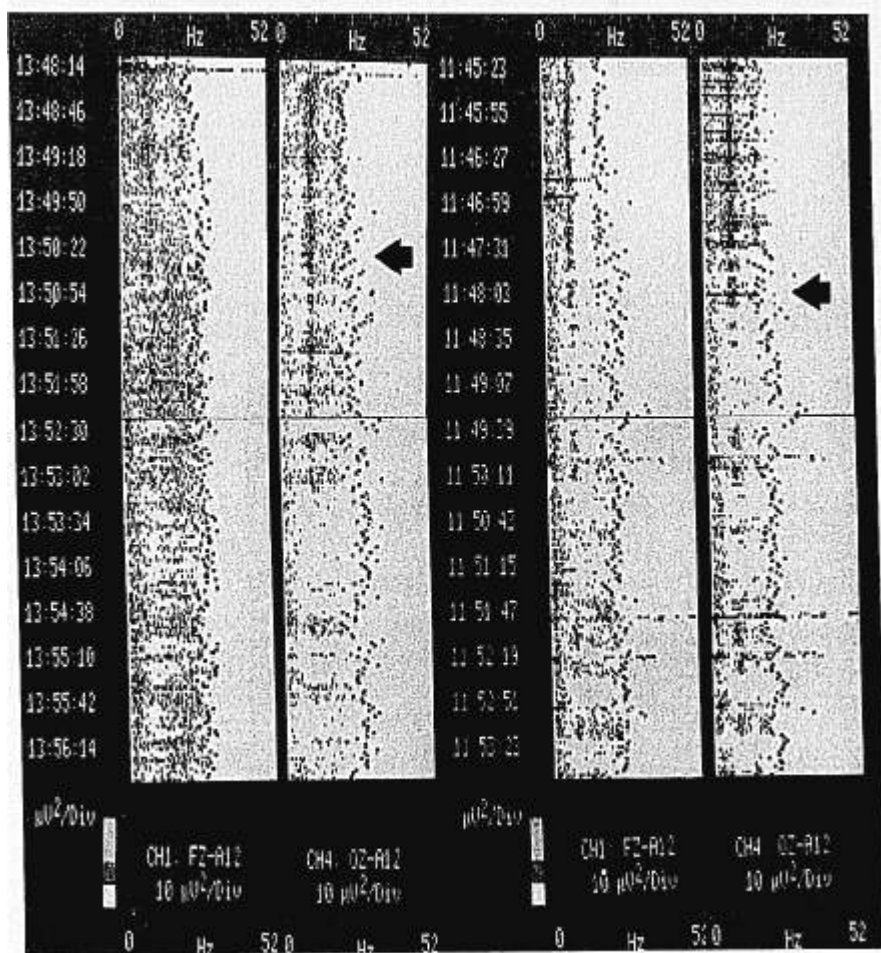


FIG. 5. Trend plot of the beta1/alpha ratio during midazolam infusion for two representative subjects (S10 [top] and S5 [bottom]). S5 demonstrates greater beta power at rest during baseline than S10, as demonstrated by a higher and more variable baseline beta1/alpha ratio. (See fig. 7 for the corresponding DSA display.) The vertical line at $t = 3.5$ indicates the onset of amnesia.

FIG. 6. Continuous DSA display during first 8.5 min of midazolam infusion from 2 subjects: S5 (left) and S10 (right). (These are the same subjects shown in fig. 5.) For clarity, only the frontal and occipital channels are presented. Time increases from top to bottom in 2-s epochs. EEG power is shown for a bandwidth of 0–52 Hz; increasing EEG power is represented by increasingly darker dots. Frontal beta activity is stronger in S5 than S10, indicating the range of intersubject variation. In both subjects the disappearance of frontal and occipital alpha activity is visible with the onset of amnesia (arrow). At this point beta power increases, principally in the anterior EEG leads.



fusion ratings, to -0.93 for the 3 postinfusion ratings. These high correlations indicate that the two VAS scales are reliably measuring the same underlying cognitive dimension.

Discussion

These observations indicate that the period of amnesia that occurs after intravenous midazolam administration can be identified by changes in the EEG power spectrum, and most specifically by changes in the beta1/alpha power ratio. Since total power was not changed, these results indicate that the primary EEG effect occurring during amnesia is a shift in power from low to high frequencies. This frequency shift was reflected in the dramatic increase in beta1 and beta2 power values (figs. 1 and 2). Although the simultaneous decreases in alpha power (fig. 3) showed only a marginally significant trend, the beta1/alpha ratio increased three-fold with the onset of amnesia (fig. 4). This change was not only statistically significant but was readily apparent when the beta1/alpha trend was displayed (fig. 5).

The greatest change in all EEG parameters coincided with the period of complete amnesia at the end of infusion. By the end of the infusion the beta1/alpha ratio had increased to its greatest value, but the change from the amnesic period of the infusion to the end of infusion was not as dramatic as the change during the 1-min transition from nonamnesia to amnesia during the infusion, occurring an average of 3.5 min after the start of infusion. Changes in spectral edge and median frequency were not nearly as remarkable as were the power shifts, and we found the former parameters insensitive to changes in power distribution occurring with light midazolam sedation.

The beta1/alpha power ratio appears to be the most useful EEG parameter in monitoring the EEG effects of light midazolam sedation. This ratio reflects the opposing changes occurring in the two frequency ranges affected most by midazolam at these serum concentrations. These results are consistent with those of Buhner *et al.*, who, in a preliminary qualitative study of hypnotic doses of midazolam, found a change in EEG power distribution, with increased power in the beta range.¹¹ They found that

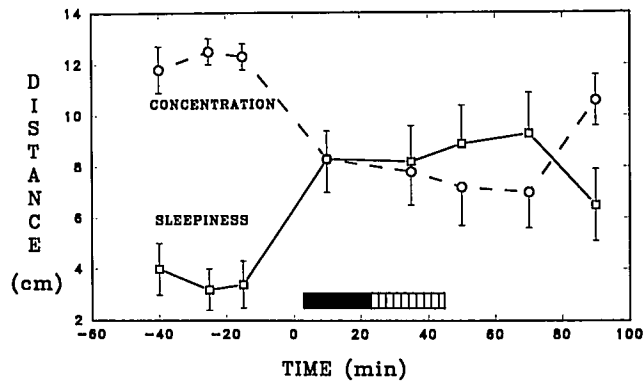


FIG. 7. Subjective ratings (mean \pm SEM) of sleepiness and concentration before, during, and after midazolam infusion. The filled portion of the bar above the x-axis indicates the duration of complete amnesia; the striped portion indicates the duration of partial amnesia. Note the large change in subjective rating during and immediately after infusion. The degree of self-reported effect remains fairly constant after this throughout most of the experiment, even though cognitive and EEG effects are changing.

spectral edge and median frequency values had inconsistent changes. Their interpretation of the data were qualitative, and no statistical analysis was performed.

Changes in EEG pattern and degree of amnesia correlate with the probable changes in serum concentration of midazolam. The largest EEG effect was obtained during complete amnesia at the end of infusion. As blood concentrations declined, subjects first experienced partial amnesia and then complete recall. EEG effects returned to baseline in a consistent fashion during this time period. In our study, partial amnesia occurred at a time when the EEG effect of midazolam was intermediate between baseline and full amnesic effect. At the end of infusion, when amnesia was complete, we found an increase in beta frequency power of 20% over baseline. Greenblatt *et al.* reported a similar increase in beta power at maximal effect during midazolam infusion producing light sedation (subjects were able to count numbers).³ Serum midazolam concentrations reported by Greenblatt *et al.* at this EEG effect were about 100 ng/ml. Serum concentrations at 50% effect (EC_{50}) were 35 ng/ml. At the equivalent beta effect in our study, partial amnesia occurred. Persson *et al.* reported the relationship of amnesia with serum midazolam concentrations after intravenous anesthesia using midazolam with or without alfentanil.⁸ They found that complete amnesia occurred at serum midazolam concentrations above 100 ng/ml and that the EC_{50} for partial amnesia in two groups of patients recovering from midazolam infusion were 64 and 81 ng/ml. Therefore, full amnesia with midazolam seems to occur when the serum concentration is greater than 100 ng/ml and when beta power in the EEG increases to 20% above baseline.

Parameters describing EEG power distribution in the

alpha and beta frequency bands change the most at serum midazolam concentrations, generally less than 100 ng/ml, that are associated with the onset of amnesic effects. Greenblatt *et al.*, using the percent increase in beta power from baseline values, found an EC_{50} of 35 ng/ml after intravenous midazolam 0.15 mg/kg. Koopmans *et al.*, using the percent decrease in alpha power from baseline values, found an EC_{50} of 46 ng/ml after 15 mg midazolam orally.⁷ Our study was not designed to model changes in EEG power distribution with measured serum concentrations, and we therefore cannot determine an EC_{50} . However, the mean serum concentration of midazolam at a time of partial amnesia, which corresponds to an intermediate effect on the EEG in our study, was 50 ng/ml. This is very similar to the serum concentrations reported by Greenblatt *et al.* and Koopmans *et al.* when EEG power distribution was changing most rapidly at the EC_{50} concentration.

Aperiodic analysis of the EEG may provide an alternative measure of midazolam central nervous system (CNS) effect. These parameters seem to have the greatest change at higher serum midazolam concentrations, which are associated with unresponsiveness. Buhner *et al.* found an EC_{50} of 152 ± 48 or 171 ± 70 ng/ml, depending on the method of estimation, after rapid intravenous infusion of 7.5, 15, or 25 mg of midazolam.¹² Breimer *et al.*, using the total number of waves from an aperiodic analysis of the EEG as a measure of CNS effect of a hypnotic dose of midazolam (15 mg), found an EC_{50} of 290 ± 98 ng/ml.⁵ EEG effects as measured by aperiodic analysis had returned to baseline by the time serum concentrations were 60 ng/ml.

We believe that amnesia was related primarily to the administration of midazolam and not to sedation. Other investigators have reached similar conclusions during benzodiazepine administration.¹³ Self-ratings of sleepiness and concentration showed a dramatic change during midazolam infusion and little change thereafter (fig. 7). These measures decreased to the middle of the range and remained unchanged for about 40 min. At 90 min post-infusion, alertness and concentration had still not quite returned to baseline levels. Thus, after midazolam infusion, VAS of sleepiness and concentration remained unchanged, despite widely varying EEG effects and degree of amnesia.

The effect of midazolam on the EEG was not uniform at all electrode sites. The significant statistical interaction between state and electrode position indicates that all EEG parameters, except delta and theta power, react differently to varying blood concentrations of midazolam, depending on where on the scalp they are measured. At baseline, alpha power was greatest in the occipital area, as would be expected in normal subjects during quiet rest and with their eyes closed. Alpha power changes were

greatest in the occipital and parietal leads, as may be expected from EEG power distribution in the baseline state. The changes in beta power with the onset of amnesia, especially in the beta2 band, were greatest in the frontal and central regions. Changes in the beta1/alpha power ratio, though of different absolute values, showed at least a three-fold increase at all electrodes. This ratio adequately reflects the major power changes occurring with midazolam administration—namely, an increase in beta power and a decrease in alpha power at all electrode sites.

These topographic changes are consistent with findings from EEG studies of other benzodiazepines.^{14,15} Studies of midazolam sedation specifically have found similar distributions of EEG power changes. Consistent with our results, French *et al.* found the maximum increase in beta activity to occur in the frontal area and the maximal decrease of alpha power to occur in the occipital region.⁶ Greenblatt *et al.* monitored all 10–20-system EEG leads and chose the left frontocentral region to obtain beta power readings, presumably because these may have reflected the greatest changes in beta EEG activity.³ However, those authors did not specifically report on topographic differences in beta power. Other investigators examining the EEG effects of midazolam in sedative doses used the frontal leads, but it is unclear if they did so because these leads represent the high-frequency EEG activity of midazolam most clearly or if these leads were the most convenient.^{4,5}

It is interesting that volatile anesthetic agents in sub-anesthetic concentrations (approximately 0.4 MAC) result in a similar EEG pattern of anterior high-frequency EEG activity with loss of alpha activity.^{16,17} In the study by Levy,¹⁷ this EEG change was apparently related to the onset of amnesia. Tinker¹⁶ suggested that the onset of anterior high-frequency EEG activity occurring with volatile anesthetics may indicate the loss of awareness. However, other agents that do not produce amnesia, such as thiopental, also produce high-frequency EEG activity.^{18,19} Further investigation is necessary to determine if the EEG patterns produced by these diverse agents are indeed similar in magnitude and topography.

These topographic differences possibly can be explained by the action of midazolam at receptor sites in the CNS. An *in vivo* positron-emission tomography (PET) scan study of human benzodiazepine receptors in four normal adults found the highest receptor binding in the occipital and frontal cortex.²⁰ In that study, uptake of the ¹¹C-labeled flumazenil reached maximum within 12 min in these cortical areas. The pronounced EEG effects of the disappearance of occipital alpha and the appearance of frontal beta observed in our study may thus directly reflect the activity of benzodiazepine receptor sites in cerebral cortex.

In conclusion, these data support a close relationship between the degree of amnesia and shifts of power in the EEG to high-frequency activity. Both EEG and amnesic effects are seemingly related to serum concentrations of midazolam. Satisfactory amnesia results when the serum concentration of midazolam is on the order of 100 ng/ml. Changes in EEG power distribution are sensitive to the CNS effects of midazolam at these serum concentrations. However, the spectral edge, median frequency, and total power parameters are insensitive measures of EEG changes occurring with the onset of amnesia. At serum midazolam concentrations associated with amnesia, the beta1/alpha ratio in the midline frontal (Fz) lead is approximately 1.0, and the beta activity is increased 20% over baseline.

Using the EEG power spectrum as a guide, administration of midazolam in a typical clinical situation may be tailored to the desired effect of amnesia in each individual patient, while avoiding the side effects of excessive sedation. Variations in individual pharmacokinetic parameters would be unimportant when midazolam is titrated to a pharmacodynamic effect as measured by changes in EEG pattern. Using this method of administration of midazolam, it may be possible to obtain a more rapid recovery from midazolam, which would be highly desirable in an out-patient surgery setting.

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