The P300 event-related potential during propofol sedation: a possible marker for amnesia?†

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Summary
We have studied the effects of conscious sedation with propofol on long latency components of the auditory event-related potential (ERP) in 10 normal volunteers (aged 21-41 yr) receiving propofol 75 μg kg⁻¹ min⁻¹ i.v. We examined the effects of propofol on ERP amplitudes and latencies, and their relationship to delayed recognition performance using a verbal memory test, a selective attention task (button pushing) and serum concentrations of propofol. During infusion of propofol, subjects were mildly sedated, oriented and readily responsive to verbal commands. ERP were recorded from monopolar Fz, Cz and Pz electrodes. We used a standard paradigm requiring selective attention to randomly occurring stimuli associated with a target stimulus (button push). The peak-to-peak amplitudes and latencies of the N2 and P3 waves were obtained before and during infusion, and 15, 100 and 170 min after infusion. Propofol produced a 70% decrease in the amplitude of P3 (P < 0.0001) from baseline and a 50% increase in reaction time. The differential response to target compared with non-target stimuli was maintained during infusion for both N2 and P3. Memory performance correlated more strongly with changes in P3 amplitude (r = 0.59) than with serum propofol concentrations (r = -0.07), although this correlation with memory did not reach statistical significance (P = 0.08). We conclude that P3 amplitude was profoundly affected by propofol given in sedative concentrations. (Br. J. Anaesth. 1995; 74: 674-680)

Key words

Previous work in our laboratory indicated that certain variables of the EEG, particularly log beta power (15-30 Hz), correlate with the presence of amnesia in subjects receiving sedative doses of propofol and midazolam [1, 2]. We wished to investigate the relationship of memory changes with more complex aspects of the EEG signal, such as event-related potentials (ERP), which are very sensitive to the effects of drugs on the central nervous system [3]. Components of the ERP waveform are affected differentially by performance of various tasks, and by administration of drugs. Early portions of the auditory ERP, occurring less than 10 ms after the elicitatory stimulus, represent neural transmission along the auditory nerve and in brain stem nuclei, and are relatively insensitive to cognitive task manipulations or to the effects of anaesthetics [4]. Middle latency auditory evoked responses (MLAER), occurring at 10-50 ms after the stimulus, show dose-related reductions in amplitude and increases in latency during anaesthesia and are currently receiving attention as possible indicators of awareness under general anaesthesia [5-7]. The long latency components of the auditory ERP (occurring more than 50 ms after the stimulus) are related to cognitive processing, and seem promising indicators of changes in cognitive function which occur during conscious sedation [8]. A typical selective attention task which elicits these long latency components is the “oddball” or deviant stimulus paradigm. The oddball tone elicits a positive peak, the P3 or P300, in the ERP, occurring about 300 ms after the stimulus (see fig. 1). This may reflect cognitive operations involved in counting or updating memory representations of the stimulus environment. Earlier negative deflections in the ERP at about 100 and 200 ms post-stimulus are labelled the N1 (N100) and N2 (N200) waves, which appear to be markers of the selective attention process [9]; these negative waves are present for both high and low tones. The psychological literature on the P3 and memory indicates a positive relationship between P3 amplitude and subsequent recall of particular stimuli [10, 11]. Sedative drugs (fentanyl, midazolam and sufentanil) seem to affect predominantly P3 amplitude, with little effect on latency [12-14]. Recent observations correlating N1 and P3 amplitudes with different depths of sufentanil anaesthesia indicate that these...
responses may be useful in identifying periods of awareness, consciousness, or both, during general anaesthesia [14].

Based on these observations, we postulated that the long latency auditory event-related responses may provide useful information on the amnesia that occurs during conscious sedation with propofol. In previous research in our laboratory, volunteer subjects receiving midazolam [12] had markedly diminished N2 and P3 components of the auditory ERP up to 50 min after termination of infusion of 0.07 mg kg\(^{-1}\) over 10 min. The reduction in amplitude coincided with a period of amnesia. The present study is based on ERP data obtained during propofol infusion in a group of volunteers. We have previously reported the EEG data from this study [1]. The ERP data we now report are not derived from the previously reported EEG data, and were obtained at different times during the study than the previously reported EEG data. Our analysis of the ERP data was designed to investigate the late components of the auditory ERP as indicators of complex cognitive processing during propofol sedation, and relate these to memory functioning. The infusion rate of propofol was sufficient to produce a state of amnesia in most subjects. Concomitantly, behavioural data (reaction time and subjective VAS scores) were obtained to assess the sedative effects of propofol. Measurements were obtained for 3 h after termination of the propofol infusion.

Subjects and methods

After obtaining Institutional Review Board approval and informed consent, we studied 10 paid volunteers (seven males) aged 21—41 yr (mean age 34.4 yr). Subjects had no history of medical or neurological problems and had fasted for at least 8 h. No caffeine was allowed on the day of the study.

After an initial bolus of 0.5 mg kg\(^{-1}\), an infusion of propofol 0.75 mg kg\(^{-1}\) i.v. was administered over a period of approximately 40—45 min. During infusion the subjects were drowsy but still responsive to verbal commands. During and after the infusion, subjects were monitored with ECG, arterial pressure and pulse oximetry.

ERP recording

Event-related potentials (ERP) were recorded during the baseline period, again at 25—30 min after the start of infusion, and at 15, 100 and 170 min after infusion. Subjects were instructed to keep their eyes closed and avoid talking or movement during recording. The analogue EEG signal was collected from Fp1, C3, and P3 electrodes referenced to linked mastoids (A1 and A2) for 900 ms post-stimulus. Electrode impedances were less than 5 k\(\Omega\). Using a Tracor Northern Nomad 3400 (Tracor Northern/Dynamic Engineering, Middleton, WI, USA) EEG monitor with online artefact rejection (based on amplitude), the EEG was sampled at 128 Hz in a bandwidth of 1—30 Hz. No electro-oculogram was obtained, but subjects were observed closely for any eye or facial movement which could affect the EEG recording, and another recording obtained if significant artefact occurred. Auditory stimuli were presented using an “oddball” paradigm, with frequent (80%: 1000 Hz) and rare (20%: 2500 Hz) tones presented at intervals of 1.5 s. Rare tones are designated as “targets,” while frequent tones are considered as “distractors,” that is, non-targets. Tones had a stimulus duration of 60 ms and were presented binaurally at 80 dB without masking noise. EEG responses to the stimulus tones were summed and averaged by the EEG monitor. Each ERP recording (“trial”) lasted approximately 6 min and terminated when 40 artefact-free rare tone responses had been collected.

Measurement of ERP amplitude and latency

For each average waveform, the N2 and P3 components were identified visually. The latency and amplitude of each component were determined by cursor placement on the ERP display provided by the Tracor Nomad 3400. Latency was measured in milliseconds from stimulus onset to the point of maximum amplitude. N3P3 amplitude was measured peak-to-peak (N2—P3) between the points of maximum negativity and positivity for that component (see fig. 1).

Selective attention task

Subjects were instructed to count the rare tones (“targets”) and press a button each time a rare tone was presented. Frequent tones (“non-targets”) were not task relevant. After the end of ERP recording, subjects were asked to report how many rare tones they had counted, and did not receive feedback on the accuracy of their count. For the reaction time measure, stimulus tones and button press responses were recorded on separate channels of a stereo cassette recorder. The reaction time (RT) was measured in milliseconds and incorrect responses (“false alarms”, that is pushing the button when a rare tone was not presented, and “misses”, that is no button push within 1 s following a rare tone) were counted.

Word recognition task

Memory performance was assessed at baseline, during infusion and 15 min after infusion by administration of the Rey Auditory–Verbal Learning Test (Rey AVLTT). As reported previously in more detail [1], on each administration the subject was given five trials to learn a list of 15 words. Recall measures were obtained on each presentation. Different word lists were used for the three tests administered. At the end of the experiment, approximately 3.5 h after the end of the infusion, subjects were given a list of 180 words and asked to circle those 90 words that had been presented on the three versions of the Rey AVLTT. The percentage of words recognized correctly was taken as the measure of memory performance for baseline, drug and recovery trials.


SEDATION RATINGS

Subjective ratings of sleepiness and concentration/attention were obtained before and after each ERP trial and averaged together. These ratings were made by placing a mark on a 15-cm line, between two anchored extremes (very wide awake—very sleepy; can’t concentrate at all—can concentrate fully). Values from infusion and post-infusion periods were compared with mean baseline VAS ratings by repeated measures ANOVA.

SERUM CONCENTRATIONS

A venous serum sample was obtained at baseline and thereafter before each ERP recording and after each administration of the Rey AVLT memory test. Each 8-ml sample was collected in a heparinized tube and centrifuged at 3900 rpm for 7 min. Plasma was separated and stored at —20 °C. Plasma propofol concentrations were measured by high-pressure liquid chromatography (HPLC). The mean was taken of three blood samples obtained during infusion of propofol (at approximately 5, 20 and 35 min) to provide a single value for use in statistical analyses. For the post-infusion recovery period, the samples obtained before ERP recording and after administration of the Rey AVLT were averaged.

STATISTICAL ANALYSIS

Missing data for one subject at the 170-min post-infusion recording were replaced with the group means for all other subjects on that trial. Measures of central tendency are given throughout as mean (SD), unless otherwise indicated. Pearson correlation coefficients were obtained among mean blood concentrations, ERP amplitude and word recognition scores, reaction time, tone count and VAS sedation ratings. A repeated measures ANOVA was computed for each ERP component (N2 and P3 latency; N2P3 amplitude). The analysis included the main effects of condition (baseline, drug, after infusion), stimulus (target vs non-target), electrode (F3, Cz, Pz) and their interactions. Probability values less than 0.05 were taken as significant. The orthogonal contrasts within the ANOVA procedure enable direct comparisons of each trial vs baseline, without increasing the risk of spuriously significant results (Type II errors); thus the Bonferroni correction is not necessary. In reporting probability values, the more conservative values of the Huynh-Feldt epsilon were given in table 1 for each ERP trial. The major effect of propofol on the ERP was a reduction in the amplitude of the P3 waveform (main effect of trial: P < 0.008) (figs 1, 2). Overall, target tones elicited higher amplitude P3 waves than non-target tones (main effect of stimulus: P < 0.001). Propofol sedation caused unexpected decreases in peak latency. While latencies of N2 decreased slightly during infusion (from 211.0 (26.9) to 187.0 (38.0) ms; P < 0.03), they returned to baseline within 15 min of the end of the infusion. P3 latency showed a slight but non-significant decrease (P < 0.10). The N1 peak amplitude and latency were unchanged during propofol sedation. However, N2P3 amplitude decreased during administration of propofol (P < 0.02). The differential response to the target tones was decreased by propofol (trial x stimulus interaction: P < 0.007). Nonetheless, target tones continued to elicit slightly higher ERP amplitudes than non-target distractors (P < 0.02). At 15 min after infusion, P3 amplitude was still significantly different from baseline (P < 0.006). Three hours after the end of the infusion, the P3 amplitude had still not returned to baseline levels (P < 0.04) (see fig. 2A).

SCALP TOPOGRAPHY

Significant variations in N2P3 amplitude were found between recording sites (main effect of electrode: P < 0.01). At baseline, the maximum amplitudes were seen at Cz. With propofol, the decrease in amplitude was more marked over anterior scalp placements (P < 0.004) than at parietal sites. However, target stimuli continued to elicit larger amplitudes during propofol sedation, and this effect was most pronounced at P3 (P < 0.04). Peak latencies did not differ between measurement sites.

WORD RECOGNITION TASK

Table 2 presents the recognition scores (percentage of words recognized correctly at the end of the study day) for each subject on the three administrations of the Rey AVLT, together with the serum concentration. Recognition scores declined from 90.0 (9.6)% for words presented at baseline to 18.7 (24.7)% for words presented during infusion (P < 0.0001, ANOVA). By the recovery test 15 min after infusion, recognition memory for words had returned to baseline levels. During learning, serum concentrations were 0.9 (0.5) μg ml⁻¹ during infusion and 0.5 (0.2) ng ml⁻¹ at the 15-min post-infusion test. The last blood sample was obtained approximately 30 min before the delayed recognition test; the concentration was 0.07 (0.01) μg ml⁻¹. Serum concentrations, whether measured during learning or at the time of delayed recognition test (3.5 h after infusion), did not correlate with memory scores.

RELATION OF ERP TO MEMORY

For the purposes of evaluating the relationship of ERP amplitude and serum concentration of propofol to memory performance, Pearson correlations were computed between measures of percentage change from baseline for N2P3 amplitude (measured at Cz), serum concentration at the time of list learning and
Propofol sedation and the P300

Table 1

<table>
<thead>
<tr>
<th>N2P3</th>
<th>Baseline</th>
<th>Infusion</th>
<th>t = +15 min</th>
<th>t = +100 min</th>
<th>t = +170 min</th>
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</thead>
<tbody>
<tr>
<td>Target</td>
<td>12.75 (7.9)</td>
<td>4.96 (2.8)</td>
<td>8.26 (4.7)</td>
<td>8.42 (1.7)</td>
<td>9.46 (4.4)</td>
</tr>
<tr>
<td>Non-target</td>
<td>2.21 (1.6)</td>
<td>2.61 (1.6)</td>
<td>1.72 (1.5)</td>
<td>2.32 (1.5)</td>
<td>1.82 (1.0)</td>
</tr>
<tr>
<td>Target</td>
<td>14.85 (10.6)</td>
<td>4.50 (2.0)</td>
<td>8.39 (6.1)</td>
<td>9.42 (4.5)</td>
<td>10.70 (7.3)</td>
</tr>
<tr>
<td>Non-target</td>
<td>2.50 (1.8)</td>
<td>2.23 (1.5)</td>
<td>1.82 (1.5)</td>
<td>2.42 (1.5)</td>
<td>1.97 (1.0)</td>
</tr>
<tr>
<td>Target</td>
<td>10.11 (5.9)</td>
<td>4.61 (2.3)</td>
<td>6.22 (3.5)</td>
<td>6.34 (3.2)</td>
<td>8.22 (4.3)</td>
</tr>
<tr>
<td>Non-target</td>
<td>2.37 (1.1)</td>
<td>1.75 (1.2)</td>
<td>1.74 (1.1)</td>
<td>2.13 (1.0)</td>
<td>2.05 (0.9)</td>
</tr>
</tbody>
</table>

Figure 1 Grand average waveform (average includes all data from n = 10 subjects) for ERP recordings made at baseline, during infusion, and 15, 100 and 170 min after terminating the infusion. The positive deflection at about 300 ms after the stimulus is the P3 peak. The dashed vertical line marked “a” represents the measurement of peak-to-peak amplitude for the N2P3 component. For each trial, the averaged ERP response at C3 is shown to rare “target” high tones (solid line) and frequent “non-target” low tones (dashed line). EEG is acquired for 100 ms before stimulus presentation at time = 0 ms (vertical dotted line) and acquisition continues for 900 ms after stimulus presentation. The P3 peak, and the negative-going slow wave (SW) which follows it, are present only for the target tones, while random responses to the non-target tones average to a flat line. Note that during infusion, N2 and P3 are markedly diminished while the N1 response remains intact, a sign that attentional processing is maintained. Recovery of the ERP waveform began rapidly after terminating the infusion of propofol but still had not reached baseline levels nearly 3 h later.

Figure 2 A: Mean (SEM) amplitude of N2P3 at the C3 electrode for ERP trials recorded before, during and after infusion of propofol. t = Duration of propofol infusion (infusion starts at t = 0). Responses to rare “target” high tones (■) vary with time of the ERP trial, while responses to frequent “non-target” low tones (□) are relatively invariant. *P < 0.05 vs baseline. B: Mean (SEM) VAS scores for sleepiness (○) and concentration/attention (●) plotted above mean (SEM) serum concentration of propofol (▲). Note that VAS ratings of concentration/attention mirror the changes in amplitude of N2P3, while VAS ratings of sleepiness parallel the changes in serum concentrations of propofol.

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the percentage of list words recognized correctly. During infusion there was almost no correlation between recognition performance and serum concentration (r = —0.20), but there was a strong trend towards a positive relationship between recognition performance and P3 amplitude (r = 0.59, P = 0.08). Thus subjects who had a greater decrease in P3 amplitude relative to baseline also showed greater decrements in recognition of words presented during the infusion.

PROPOFOL SERUM CONCENTRATION

Mean values for serum concentrations of propofol during and after infusion are shown in table 2 and figure 2b. At the time of learning the Rey AVLT word list during infusion, serum concentrations varied from 0.37 to 1.85 µg ml⁻¹. At the time of
ERP recording during the infusion, approximately 20 min later, concentrations varied from 0.52 to 1.63 μg ml⁻¹. The serum concentration of propofol reached a maximum of 1.14 (0.39) μg ml⁻¹ by the end of infusion. While serum concentrations did not maintain a perfect steady-state concentration over the 45 min of the infusion, the trend towards increasing plasma concentrations during infusion was not significant by ANOVA (P = 0.09) or by a corresponding non-parametric test (Friedman two-way analysis of variance using ranks). Serum concentrations during the post-infusion period varied from 0.30 to 0.87 μg ml⁻¹ during recording of ERP 15 min after infusion and from 0.29 to 0.93 μg ml⁻¹ during learning of the Rey AVLT word list. During infusion, correlations between propofol serum concentrations and P3 amplitude were on the order of r = +0.10 (ns). During the recovery period, P3 amplitudes showed a better correlation with serum concentration (r = −0.56) but they still did not reach statistical significance with this small sample size (P < 0.12). This negative correlation indicates that higher serum concentrations were associated with lower P3 amplitudes.

SEDATION RATINGS

Compared with baseline values, sleepiness increased (P < 0.001) and concentration/attention decreased markedly (P < 0.0004) during drug administration, reaching their maximum by the end of infusion (see fig. 2b). Immediately after termination of the infusion, these sedative effects began to decline, but did not return to baseline levels for more than 1 h after the infusion ended.

SELECTIVE ATTENTION TASK

The percentage of target tones counted (count %) by the subjects declined from a mean of 100.8 (12.2)% at baseline to 76.3 (24.2)% (P = 0.03) during infusion. This represents a 24% decrease in vigilance performance during sedation. Fifteen minutes after the infusion ended, counts were again 97.9 (5.9)% correct. There was no consistent relationship between count % and serum concentrations. Subjects’ counting performance was much more variable during infusion (range 44–150 % tones counted). (Counts of more than 100 % occur when subjects’ counts exceed the number of tones actually presented.) RT data were available for nine subjects. RT to target tones increased by 50% during sedation, from 350 (86) ms to 524 (127) ms after administration of propofol (P < 0.004). Performance accuracy was also affected; the mean number of missed target tones increased from 0.6 at baseline to 9.1 during infusion, and the number of false alarms increased three-fold, from 1.2 at baseline to 3.7 during infusion. By 15 min after infusion, RT was no longer significantly different from baseline. RT to correctly detected targets showed no correlation with serum concentrations or P3 amplitude and latency.

Discussion

HOW PROPOFOL AFFECTS THE AUDITORY ERP

Previous investigations

To our knowledge, the relationship of the P3 to propofol administration, either during sedation or full anaesthesia, has not been investigated previously. Several investigators have studied the earlier components of the auditory ERP, arising from the brain stem, or primary auditory cortex. Brain stem components have been affected as little by propofol anaesthesia as by other anaesthetic agents [4, 15, 16]. Propofol affects the middle latency components (10–50 ms after stimulus presentation) more substantially. The amplitude of these middle latency components is related to the dose of propofol administered [16, 17], and they are still present during general anaesthesia with propofol. Spectral analysis of the middle latency evoked response (20–100 ms post-stimulus) reveals that the 30–40 Hz component of the power spectrum is suppressed by propofol in anaesthetic doses. The component is thought to be related to conscious sensory information processing [18–20].
The findings of the present study indicated that propofol in sedative doses had a strong effect on the amplitude of the ERP components occurring more than 100 ms after the stimulus. P3 amplitude was reduced to 30% of baseline during propofol sedation, but was still significantly larger than the response to non-targets. In contrast with the usual maximum at Pz, P3 amplitude during propofol infusion showed a more anterior distribution. This may reflect the topographical gradient of electrophysiological effects of propofol during sedation, as an anterior shift of EEG beta activity also occurs [1]. The decrease in P3 amplitude coexisted with a 24% decrease in overall accuracy in the selective attention task, and a relatively much larger decrement in memory performance, which decreased from 90% to less than 20% of words recognized.

RELATION OF P3 TO MEMORY PERFORMANCE

Although we could only demonstrate a trend, the results of this study indicate that a specific measure of end-organ effect (i.e. the EEG as specifically represented by the P3 event-related potential) was a more reliable indicator of CNS state than serum concentrations of propofol. Venous serum concentrations of propofol correlated poorly not only with memory performance, but also with the behavioural measures of the P3 paradigm (RT and count %). Unfortunately, even though the correlation (r = 0.59) between N2P3 amplitude and memory performance was much stronger than any other correlations examined, statistical significance was not achieved (P = 0.08), possibly because of the small number of subjects examined or, more likely, the ERP was recorded separately from the memory test (the equipment used in this study did not allow us to perform these tests simultaneously). The separation in time between ERP recording and memory test would diminish the relationship of P3 amplitude with memory performance, particularly when brain concentrations of propofol are decreasing rapidly after the end of infusion (where we found no correlation between P3 and memory performance). Larger correlations are typically obtained when ERP are recorded simultaneously with presentation of individual words [10, 21-23].

We conclude that the P3 component of the long latency ERP was affected profoundly by propofol when administered in sedative doses. As the P3 represents complex information processing, it may be a useful marker of cognitive impairment during periods of sedation. This impairment in cognitive functioning may relate to the formation (or lack thereof) of lasting memories. Although we were not able to demonstrate statistical significance, P3 amplitude was the most promising of all of the measures (including serum propofol concentrations) examined in this study related to the process of propofol-induced amnesia. Thus further investigation is required of the relationship of P3 to memory functioning during administration of sedative agents associated with “amnesia” (midazolam, propofol), and those not associated with “amnesia” (fentanyl or other opioids).

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