Alteration by Enflurane of Electrophysiologic Correlates of Search in Short-term Memory

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Effects of controlled subanesthetic concentrations of enflurane on short-term memory functions and associated scalp evoked potentials were studied in eight male volunteers. Short-term memory processes were assessed through a search task. A series of digits (one, three, five, seven, nine, or 11 digits in each series) was presented visually, followed by a test digit, which in half of the trials was part of the series, and in half of the trials was not. The subject responded by pressing one of two switches, signalling "yes" or "no" accordingly. Averaged evoked potentials elicited by the test digit were obtained from seven sites on the scalp.

End-tidal enflurane concentrations between 0.12 and 0.25 per cent increased significantly by 30–40 msec the latency of the components of the evoked potentials reflecting sensory processing, but did not affect their amplitude significantly. This increase could not explain the 297-msec increase in reaction time. Amplitude of late components of the averaged potential reflecting information processing was markedly decreased, which the authors interpret as indicating increased trial-to-trial variation in latency of the late component. The authors conclude that enflurane delays and introduces variance into the short-term memory processes and subsequent decision processes that precede overt responses. (Key words: Anesthetics, volatile: enflurane. Brain: electroencephalography; evoked potentials. Memory. Toxicity; trace concentrations.)

The psychological effects of subanesthetic concentrations of general anesthetics may interest anesthesiologists for three main reasons. First, since anesthetics affect various functions in a dose-dependent manner, psychological changes resulting from subanesthetic doses are indicative of the types of effects that might occur after exposure to trace anesthetic concentrations such as those found in the operating room atmosphere. Unfortunately, available behavioral tests may not be sensitive enough to detect effects produced by minute doses of gases. Second, such studies indicate possible long-term effects of chronic exposure to trace anesthetic concentrations. Third, such studies indicate what cognitive deficits may be expected in patients recovering from surgical anesthesia. In this paper we report a study on the effects of controlled subanesthetic doses of enflurane on search for information in verbal short-term memory and its electrophysiologic correlates in man, as reflected in the averaged evoked scalp potential.

We have previously shown that subanesthetic concentrations of various inhalational anesthetics have dose-dependent effects on long-term memory, ranging from temporary difficulties in assessing learned verbal material at very low concentrations to complete, permanent amnesia at higher concentrations. Since long-term memory depends on effective processing of information in short-term memory, we chose to investigate the short-term memory process.

The best known index of short-term memory function is the short-term digit span. Although Bruce and his group have reported finding a decreased short-term memory span with trace anesthetic concentrations, we have not observed a significant effect on the span at much higher concentrations. We believe that Bruce’s results are based on a combined measure of both forward span and backward span (i.e., repeating in reverse order the presented digits), and backward span involves other cognitive operations in addition to pure short-term memory. This, we think, accounts for the discrepancy. This should not be interpreted as indicating a lack of effect on the ability to sustain attention. Possible effects of general anesthetics on short-term memory should, therefore, be validated with another test.

In this study we have assessed search in short-term memory through a well-tested task, in which the subject sees many series of digits, each series followed by a test digit to which the subject responds with “yes” if it was part of the series and “no” if not. Lengths of the series usually ranged from one to nine digits. The plot of reaction time as a function of series length is a good measure of speed of search. Furthermore, we have recently shown that the averaged scalp evoked potential (i.e., the change in the ongoing EEG evoked by a peripheral stimulus) reflects accurately the search process. We, therefore, recorded the scalp potential evoked by the search process as a tool to elucidate the electrophysiologic events underlying the psychological effects of the anesthetic. For a comprehensive review of previous uses of averaged evoked potentials in anesthesia research, see Clark and Rosner and Rosner and Clark.
Method

Subjects of study were eight healthy male volunteers more than 21 years of age, who were paid for participation. Each subject was given a full explanation of the study and the hazards involved in the inhalation of subanesthetic doses of enflurane, and was asked to give his consent to participate a few days later. He then underwent a complete physical examination and laboratory analyses that included a complete blood count; urinalysis; blood urea and determinations of glucose and serum glutamic oxalacetic transaminase values; roentgenogram of the chest, and electrocardiogram. Only volunteers whose values were within normal ranges were accepted as subjects.

In each trial the subject saw a warning signal, followed 500 msec later by a computer-generated series of digits (set), followed 500 msec later by a second warning signal. Then 800 msec later the subject saw a test digit, which stayed on for 1,500 msec. In half of the trials the test digit appeared and in half it did not. The subject responded with "yes" or "no," accordingly, by pressing a microswitch. Each subject received only one set size (one, three, five, seven, nine, or 11 digits), 80 presentations under control conditions and 80 presentations during inhalation of enflurane. The digits (1.7 cm wide × 2.4 cm high) were presented on a Tektronix oscilloscope (green phosphor) in a darkened room, at eye level, 1.90 m from the subject.

The electroencephalogram (EEG) was recorded through silver–silver chloride biopotential electrodes attached to the scalp over left and right temporal (T3, T4), left and right central (C3, C4), vertex (Cz), midline parietal (Pz), and midline occipital cortex (Oz) regions. The EEG was differentially amplified (time constant 1 sec and upper half-amplitude frequency 40 Hz) and recorded on a 14-channel FM tape recorder for later off-line computer analysis. Eye movements were recorded simultaneously on another tape-recorder channel. A trigger pulse for initiation of digital sampling of EEG by the computer synchronous with presentation of the test digit was recorded on another channel. Trials yielding correct "yes" responses were averaged separately from trials yielding correct "no" responses. Each average was based on 30–40 good trials, i.e., free of eye movement and other muscular-activity artifacts.

After control testing, inhalation of enflurane in air was started. Each subject inhaled two concentrations: 0.1–0.3 per cent and 0.4–0.7 per cent end-tidal. Our criterion for discriminating between the two doses was based on previous findings indicating amnesia for verbal material for the higher concentration but good recall at the lower concentration. Four subjects inhaled the lower concentration first and four subjects inhaled the higher concentration first. Testing was begun when equilibrium between end-tidal and inspired concentration was achieved (difference not greater than .02 per cent). End-tidal enflurane concentrations were measured using a thermal conductivity gas chromatograph (Hewlett Packard Model 5720A). Enflurane was vaporized in a Foregger Copper Kettle® and delivered through a scavenged nonrebreathing system. The subject breathed through a mouthpiece connected to a Rahn end-tidal sampler. During control testing the subject breathed air through the mouthpiece, in order to equate testing conditions to the anesthetic condition.

Statistical analysis of the data was by analysis of variance or Student t test. $P < 0.01$ was regarded as significant.

Evoked potential components were named according to their polarity and latency, i.e., a positive peak at 174 msec latency would be referred to as P170, where
the P denotes the positivity relative to the baseline, and the 170 denotes the rounded-off peak latency, according to international conventions.

**Results**

**Electrophysiologic Data**

An example of the evoked potential as a function of series length for one subject is shown in figure 1. There was a progressive differentiation of the late positivity (marked by a dot) with increasing lengths to the seven-digit set-size and again decreased differentiation for nine and 11 digits, probably indicating changes of cognitive strategy. Mean latencies and standard deviations for the early components at the vertex electrode were: negative peak at 96 msec ± 16.2 msec (N90) and positive peak at 174 msec ± 9.2 msec (P170). One-digit series yielded just one late positive component at 362 msec ± 29 msec (P360). As series length increased the latency of the late positivity increased, uncovering a positive peak at 258 msec ± 9.3 msec (P250), and a second positive peak the latency of which changed as function of series length in parallel to changes in P360.

Enflurane concentrations between 0.12 and 0.25 percent somewhat, but not significantly, enhanced P170.
and P250 amplitudes by averages of 3.2 and 2.2 μV, respectively, and significantly increased their latencies by 33 and 36 msec, respectively (fig. 2). The marked decrease in amplitude of the later parts of the traces prevented latency and amplitude measurements of the late positive component.

Higher concentrations affected attention to such an extent that not enough trials were secured for averaging. The vertex (Cz) and/or parietal (Pz) placements gave maximal amplitudes for the late components, as is well documented in the relevant literature. The early components were, in addition, also maximal over the occipital electrode, as is expected with visual stimuli. Enflurane affected all placements similarly.

**Behavioral Correlates**

Low concentrations of enflurane significantly increased mean reaction time by an average of 287 msec (range 72 to 613 msec), and also its variance (table 1). Since reaction time in such a task is highly correlated with latency of the late positivity of the evoked potential, increased variance in reaction time probably resulted in increased variation in latency of the late positivity from trial to trial. The latter could in fact lead to flattening of the late positivity in the averaged trace, due to the averaging technique. Alternatively, the averaged trace may reflect real disappearance of all late components. Since averaging is needed to extract the signal from the background EEG noise, we have to rely on two pieces of indirect evidence to support the increased-variance interpretation. First, in all anesthetic records the trace after 280-msec latency was not totally flat but showed a slow positive change that peaked before the occurrence of the motor response (table 1, last column). Second, it is usually found that when EEG sampling is locked to the motor response rather than to the stimulus, the late positivity has an amplitude much lower than that for stimulus-locked averages. We found the same trend for control response-locked averages (fig. 3). However, response-locked averages for the anesthetic condition had higher amplitudes at the latency region of the late positivity than stimulus-locked averages, indicating again that the late positivity did not disappear but rather was less time-locked to the stimulus than in control testing, and probably of smaller amplitude.

**Discussion**

Low concentrations of enflurane did not decrease significantly the short-term digit span, but slowed down by several hundred milliseconds the cognitive processes involved in search through short-term memory and the final decision leading to the motor response. The magnitude of the effect depended on the individual subject. We have shown that comparable concentrations of enflurane transiently affect the accessibility to verbal items stored in long-term memory. Since efficient retrieval of items from long-term memory depends on efficient organization of incoming material during the perception stage, the deficits in short-term processes observed in the present study can explain the deficits in long-term memory observed under anesthetic influence. Thus, the drugged subject fails to process effectively verbal information while

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**Table 1. Summary of Data for Control and Anesthetic Conditions**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Length</th>
<th>Mean Reaction Time ± SD (msec)</th>
<th>End-trial Concentration (Per Cent)</th>
<th>Percentage of Errors</th>
<th>Peak of Late Positive Process (msec)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>Anesthetic</td>
<td>Control</td>
<td>Anesthetic</td>
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<tr>
<td>Subject 1</td>
<td>1</td>
<td>494 ± 94.2*</td>
<td>1,107 ± 145.4</td>
<td>.19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>419 ± 86.6</td>
<td>1,177 ± 147.3</td>
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<td>Subject 2</td>
<td>3</td>
<td>966 ± 79.9</td>
<td>1,384 ± 311.8</td>
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<td>954 ± 96.2</td>
<td>1,325 ± 242.5</td>
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<tr>
<td>Subject 3</td>
<td>3</td>
<td>743 ± 67.5</td>
<td>1,018 ± 221.8</td>
<td>.257</td>
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<td>715 ± 78.6</td>
<td>928 ± 207.7</td>
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<tr>
<td>Subject 4</td>
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<td>776 ± 68.3</td>
<td>982 ± 186.1</td>
<td>.246</td>
<td>1.5</td>
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<td>819 ± 102.2</td>
<td>932 ± 116.4</td>
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<td>Subject 5</td>
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<td>692 ± 90.4</td>
<td>974 ± 282.0</td>
<td>.251</td>
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<td>607 ± 83.0</td>
<td>1,083 ± 194.3</td>
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<td>Subject 6</td>
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<td>734 ± 76.3</td>
<td>1,021 ± 153.1</td>
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<td>Subject 7</td>
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<td>683 ± 82.5</td>
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<td></td>
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<td>781 ± 91.4</td>
<td>933 ± 221.3</td>
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<td>Subject 8</td>
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<td>1,077 ± 138.8</td>
<td>1,149 ± 182.9</td>
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<td></td>
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<td>880 ± 159.3</td>
<td>1,024 ± 210.3</td>
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</tbody>
</table>

* Upper row shows correct "yes" responses; lower row shows correct "no" responses.
ENFLURANE EFFECTS ON EVOKED POTENTIAL

it is still in the short-term memory, resulting in registration of the material in long-term memory in a form not compatible with easy and efficient retrieval. This statement implies that while irrelevant information may be lost permanently, information that arouses motivation during the processing stage may be remembered. This may relate to alterations of auditory perception during general anesthesia.8

The anesthetic effect was reflected in the average evoked potential as increased latency of the order of several tenths of a millisecond of the components to 250 msec in latency and a marked decrease of all later components. We believe that this flat appearance of the record of the later part of the averaged potential resulted from increased trial-to-trial variability in the latency of the late positive components, and was therefore an artifact of the averaging process. These late positive components have been shown to be related in normal man to various aspects of cognitive processing of information,9,10 whereas the earlier components reflect primary cortical reception. That the anesthetic slowed the reaction time by an average of 287 msec, whereas the latency of the first components increased by only 30–40 msec, implies that most of the anesthetic effect is explained by slowing of the final stages in information processing.

Daily exposure to trace anesthetic concentrations may result in permanent deficits in functions such as that observed in our study. It is, however, extremely difficult to isolate such effects, since a subject must serve as his own control and we lack data for operating room personnel prior to anesthetic exposure. We thus need a measure that can discriminate between exposed and non-exposed groups despite individual differences in performance. The present study indicates that increased variability in the latency of the late positive components of the averaged evoked potential may serve to detect effects of chronic exposure to anesthetics.

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References

![Graph](http://example.com/graph.png)