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Indirect Memory during Anesthesia

The Effect of Midazolam

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Background: **The preservation of implicit memory function during anesthesia is controversial, with conflicting results appearing in the literature. This study was designed to elucidate the effect of midazolam as part of an anesthetic technique on implicit memory function during anesthesia. Using a prospective randomized, double-blind study design, performance in three tasks (category generation, free association, and homophone spelling) was assessed.**

Methods: **Forty-eight consenting patients were assigned to two equal groups, to receive 2 mg intravenous midazolam or normal saline before induction of anesthesia. Anesthesia was induced with fentanyl and propofol and maintained with isoflurane 1.3 MAC until incision and isoflurane 1.0 MAC in 70% nitrous oxide thereafter. Fentanyl was used for supplementation of anesthesia. During anesthesia, one of two 50-min tapes containing the test material was played to each patient on a portable cassette player. In the postanesthesia care unit and 48 h after surgery, patients were engaged in three tasks by an observer unaware of the treatment group or tape.**

Results: **No significant main effect of priming or midazolam was observed in any of the tasks. In the word-association task, an interaction was observed between priming and treatment group ($F = 9.62$, $P < .01$) due to negative priming in the placebo group.**

Conclusions: **The lack of a main effect of priming in any of the three tasks is consistent with the conclusion that indirect memory was not demonstrated for events occurring during the standard anesthetic conditions of this study. Further, midazolam appeared to have no effect. (Key words: Anesthesia: general. Memory: indirect. Hypnotics, benzodiazepines: midazolam.)**

THE search for evidence of information registration under anesthesia has been renewed by the use of indirect techniques for studying memory. With these techniques, registration may be inferred by showing the effects of prior experiences of which the subject is not aware. Indirect or implicit tests of memory[1] have been used with dramatic success in the study of organic amnesia[2] and are well suited for studying memory for intraoperative events, since conscious recollection following surgical anesthesia is rare.[3] In contrast to the findings in organic amnesia, however, the study of memory for events encountered while anesthetized has yielded a decidedly mixed set of experimental outcomes.[4]

The purpose of the present study was to examine whether some of the discrepant outcomes in the literature on anesthesia and memory may be attributed to the uncontrolled effects of preanesthetic administration of benzodiazepines. The benzodiazepines are used widely in anesthesia as sedatives and are known to have amnestic properties.[5]

While there is some evidence that implicit memory is spared following benzodiazepine administration,[6] other investigators have found contradictory results with diazepam affecting category generation but sparing word completion performance.[7] These studies were performed on healthy volunteers, and it is not clear that these results can be generalized to the use of benzodiazepines as part of an anesthetic technique. This study was instigated by the observation that recent reports of registration during surgery often are characterized by the absence of benzodiazepine premedication,[8–10] whereas studies not finding evidence of implicit memory tend to report using premedication by benzodiazepines.[11,12] We are unaware of any research on memory and anesthesia in which this factor was manipulated. In many of these studies, the intraoperative anesthetic regime has not been well controlled.[4] Either different agents have been used or the doses have not been well controlled.

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In this study, three implicit memory tasks were used: *free association,* in which subjects are asked to produce the first word that comes to mind when presented with a stimulus word; *category member generation,* in which subjects are asked to produce instances of common categories such as vegetables or animals; and *homophone spelling,* in which subjects are asked to spell words that are pronounced identically, but have different spelling and meaning (*e.g.*, fair, fare). For each task, subjects were primed with appropriate responses during surgery. Performance on all three tasks was measured in the postanesthesia care unit and 48 h after anesthesia in patients who had been anesthetized using a standardized technique, with or without midazolam.

Methods

After approval by the Human Investigation Committee, informed consent was obtained from 48 patients scheduled for elective surgery. Criteria for inclusion were age (18–60 yr), ASA physical status 1–3, and fluency in written and spoken English. Patients with hearing impairment, known cerebrovascular or neurologic disease, drug addiction, or psychiatric disorders were not included in this study.

At the time of consent, patients were informed that a taped message of neutral words would be played during anesthesia and that follow-up would consist of a question-and-answer session approximately 2 h and 48 h postoperatively.

A waterproof auto-reverse tape player (Sony WM-A53) with headphones was used to play one of two 50-min tapes. Each tape consisted of three types of verbal material. There were 10 homophones that were biased to their less common spelling (*e.g.*, garage-*sale,* movie-*reel*). The homophones were taken from published norms[13] and were selected according to the same criteria used by Eich.[14] Both spellings contained the same number of letters, and the probability of spelling a homophone in line with the less common interpretation was between 0.10 and 0.40. The tape also contained 20 word pairs taken from published free-association norms.[15] There were 10 word pairs with low (M = 20.4%) primary-response frequencies (*e.g.*, stove-*hot,* river-*water*) and 10 word pairs with high (M = 46.6%) primary-response frequencies (*e.g.*, long-*short,* boy-*girl*). Finally the tape contained two categories with four exemplars each (*e.g.*, four-footed animals: *lion, elephant, deer, zebra*). The exemplars chosen were from frequency ranks 5, 7, 12, and 16 within each category.[16]

Each of the two tapes contained a completely different list of words. The tapes were balanced on normative characteristics for the homophones, free association, and category exemplars. The tapes were blocked so that the entire set of a particular type of verbal material (*i.e.*, homophones, word pairs, category exemplars) was presented before another type was presented. Each particular stimulus set was presented 22 times, distributed throughout the 50 min of play.

The patients received oral 150 mg ranitidine and 10 mg metoclopramide the morning of surgery. Before their arrival to the operating suite, they were randomly assigned to one of two groups. Group 1 (n = 24) received 2 mg intravenous midazolam and Group 2 (n = 24) received 2 ml intravenous normal saline (double-blind). Following administration of midazolam or normal saline and 3 μg/kg fentanyl, induction of anesthesia was with 2.5 mg/kg propofol. Anesthesia was maintained with 1.3 MAC (age-adjusted) isoflurane until incision and then 1.0 MAC isoflurane in 70% nitrous oxide until the end of surgery. If required, fentanyl was administered in 50–100-μg increments to supplement anesthesia.

After incision, the cassette player was started and allowed to run continuously until the operative procedure was complete. To be included in the analysis, patients had to receive at least one complete presentation of the tape and no more than three presentations of the tape.

On preparation for discharge from the postanesthesia care unit, memory for the verbal material played during surgery was tested. In the homophone task, patients were asked to spell 10 homophones. Patients also were asked to spell three words that were not homophones. These words were distributed throughout the homophone list and were included to make it less obvious to patients that the rest of the words were homophones. The free-association task asked patients to give the first word that came to mind when presented with a word. This was conducted for 20 words. In the category generation task, patients were given 20 s to provide as many examples of a category that they could. Two categories were tested. The entire procedure took approximately 10 min. All patients were seen in their rooms approximately 48 h after surgery, and a second test session was carried out.

At each testing time, half of the responses patients could provide were presented during surgery (primed words) and half of the responses patients could provide were not previously introduced (nonprimed words). Thus, patients were their own controls. Two tapes were created to counterbalance the primed and the nonprimed words. For example, if a patient was primed with the words on the first tape during surgery, then the words on the second tape (not previously introduced to the patient) served as the nonprimed words. Half of the patients were primed with each tape. Different words were tested for each subject in the postanesthesia care unit and at 48 h.

Three task orders were used so that each task occurred first, second, and third for different patients. Task order, tape, and delay were all counterbalanced such that all possible combinations of the three task orders, the two study tapes, and the two delays occurred in both study groups (midazolam, no midazolam). The investigator who administered the postoperative testing was blind to the tape played during surgery and to the preoperative administration of midazolam or normal saline.

All statistical analyses were done with analysis of variance. Each task was analyzed separately with a 2 × 2 × 2 analysis of variance. A P value $< .05$ was considered significant. Drug group (midazolam, no midazolam) was a between-subjects factor, delay (short, long) was a within-subjects factor, and exposure to taped material (prime, no prime) was a within-subjects factor.

Results

The patients' responses were examined for the extent to which intraoperative exposure to taped words influenced postoperative performance on the three tasks. Higher numbers in the primed compared to the nonprimed condition would have provided evidence of priming from exposure to taped material. The percentage of correct responses for each task are given in table 1 with the free-association data collapsed across frequency. No significant main effect of priming or midazolam was observed in any of the tasks. There was a numeric effect of priming in five of the tasks in the early test period, but an overall analysis, using task as a within-subjects factor, showed no main effect of priming ($F < 1.0$, $P > .10$). There was a significant interaction between priming and treatment group in the free-association task ($F = 9.62$, $P < .01$), that appears to be due to negative priming in the placebo group. There were also two main effects not involving priming or midazolam. There was a main effect of response frequency in the free-association task ($F = 289.77$, $P < .001$). No other effects of response frequency were significant. This effect was not surprising as, by definition, high frequency associates are more likely to be given than low frequency associates. The other main effect involved delay in the category generation task ($F = 9.63$, $P < .01$). Fewer category exemplars were given at the short delay than at the long delay. This can be attributed to the fact that the category generation task, unlike the two other tasks, is a timed task. Patients were slower to respond a few hours after surgery because they were still sleepy following anesthesia. Forty-eight hours after surgery, this effect was not present.

Discussion

Implicit memory refers to a diverse collection of memory phenomena that do not require conscious recall. Implicit memory tests may be sensitive in the de-

Table 1. Percentage of Correct Responses

	Recovery		48 h	
	Prime	No Prime	Prime	No Prime
Category				
Midazolam	22.9 ± 22.0	16.7 ± 14.0	30.2 ± 28.5	30.2 ± 27.5
Placebo	16.7 ± 19.0	14.6 ± 20.7	30.2 ± 24.4	20.8 ± 20.4
Homophone				
Midazolam	28.3 ± 21.2	24.2 ± 16.7	20.0 ± 14.5	30.8 ± 23.6
Placebo	25.8 ± 16.1	23.3 ± 19.3	25.8 ± 18.2	19.2 ± 19.1
Association				
Midazolam	36.7 ± 18.8	33.3 ± 14.9	39.2 ± 12.5	37.5 ± 14.2
Placebo	33.7 ± 13.5	39.2 ± 12.8	31.7 ± 15.2	37.1 ± 15.2

Values are mean ± SD.

tection of information registered subconsciously during anesthesia as demonstrated by facilitation of task performance without conscious or intentional recollection of actual events. Investigators have studied amnesic patients to determine the best method to retrieve information not consciously available. Through this work, it was suggested that there may be two different retrieval routes for human memory.[17] Patients with anterograde amnesia demonstrate memory storage with implicit but not explicit memory.[2] As a result of these findings, tests of memory not requiring conscious recall of a specific learning episode became a useful tool in the study of intra-anesthetic learning.

The purpose of this research was to determine whether some of the discrepancies in the literature on memory and anesthesia could be resolved by investigating the possible modulation of priming by benzodiazepine premedication. An outcome showing priming with at least some of the three memory tasks used when no midazolam was administered, and no priming following midazolam administration, would have supported these speculations. The results, however, are clear in showing no evidence of information registration at all; with or without midazolam, there was no firm evidence of implicit memory on any task. Our negative findings are at odds with those of several previous studies. Kihlstrom *et al.*[8] reported evidence of indirect memory following anesthesia with the free-association task, and Roorda-Hrdlickova *et al.*[18] found a similar outcome with category generation. Neither of these studies report premedication with benzodiazepines. On the other hand, two experiments have reported negative results with homophone priming.[12,19] In both of these studies, benzodiazepines were administered. This pattern of results formed the basis for the present study.

In our group of patients who did not receive benzodiazepines, we were unable to replicate the positive findings of Kihlstrom *et al.* (who used isoflurane in oxygen anesthesia)[8] or Block *et al.* (who used nitrous oxide with opioids and with isoflurane),[9] although it should be noted that different tests of implicit memory were used in the three studies. Kihlstrom and colleagues also were unable to replicate the findings of their original study using a sufentanil and nitrous oxide anesthetic technique,[20] which they suggest may be due to a differential effect of anesthetic agents. However, their results may represent a failure to replicate an earlier study rather than a true difference in the effects of two anesthetic combinations on implicit memory function. Our study design avoids this problem, but we failed to establish that implicit memory function is retained during our controlled anesthetic technique.

It is possible that the administration of nitrous oxide produces a conflicting effect in these studies. Positive findings that occurred in the free-association task without using nitrous oxide[8] did not occur when nitrous oxide was part of the anesthetic technique.[20] In this study, we found negative priming in the free-association task. Negative priming in the free-association task also has been found in volunteers breathing 30% nitrous oxide.[21]

Whether adequacy of anesthesia is relevant in studies of memory function during anesthesia is controversial. Positive results have been obtained by using a tape played approximately 5 min before the "reversal" of anesthesia.[22] It is likely that the patients were lightly anesthetized during this time, and it is therefore not surprising that information registration occurred. Block *et al.* suggest that memory function occurs independent of anesthetic method or "depth" of anesthesia.[4,9] We believe that this is unlikely. Awareness and recall are more likely to occur under inadequate anesthetic circumstances,[4] and it is possible that the same is true of implicit memory. The technique used in this study was designed to provide adequate anesthetic concentrations. Fentanyl (3 μg/kg) will reduce MAC by approximately 50%[23] so, at skin incision, patients were receiving approximately 1.8 MAC equivalents of anesthesia. The findings of this present study suggest that, under these conditions of adequate anesthesia, implicit memory does not occur.

The failure to find a priming effect in the present research, along with negative findings we have reported elsewhere using a preference task,[24] only highlights the perplexing nature of research into memory and anesthesia. Until more is known about the determinants of memory for intraoperative events, it is important to pay attention to negative as well as positive findings.

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