

## **SEDATIVE AND AMNESIC EFFECTS OF MIRFENTANIL**

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### **INTRODUCTION**

Mirfentanil, an investigational new drug, is a piperidine derivative intended for use in local and regional anesthesia.<sup>1</sup> Although animal and human studies show it to have lower analgesic potency than fentanyl, a variety of studies also indicate that it is less prone to negative cardiac, respiratory, and hemodynamic side effects such as respiratory depression, bradycardia, and hypotension.<sup>2</sup> Because the preclinical studies indicated that mirfentanil had considerable potential as both a sedative and an analgesic, the manufacturer commissioned an open-label dose-ranging study of the drug's effects in humans. Because of our interest in amnesic effects, we added a series of memory tests to the manufacturer's protocol.

### **METHOD AND RESULTS**

A total of 14 patients scheduled for outpatient elective surgery (eg, orthopedic, gynecological) under conscious anesthesia (subarachnoid blockade) participated in this study. Before, during, and after surgery the patients received a series of tests of sedation (deleting the letter 'P' in a matrix of random letters and a digit-symbol substitution task) and amnesia (yes-no recognition memory for pictures of common objects). It was not possible for all subjects to receive all tests: Numbers of patients vary from 10 to 12.

Two baseline tests of sedation, P-Deletion and Digit-Symbol Substitution, were administered prior to surgery. The subjects were also shown a set (Set A) of 20 pictures of familiar objects, one at a time, and asked to name them. This was followed by a serial subtraction task. Mirfentanil was administered to the point of slurred speech. Then the patient was administered the first yes/no recognition test, consisting of 10 items from Set A and 10 matched lures, and asked to indicate which, if any, of the pictures had been shown previously. Then the patient was shown a second set (Set B, matched to Set A), as before.

*Sedative and Amnesic Effects of Mirfentanil*

The P-Deletion and Digit-Symbol Substitution tests were repeated at intervals of 15, 30, 60, 90, and 120 min after entry to the post-anesthetic care unit (PACU). Following the first post-surgical sedation tests, the patient was administered the second and third recognition tasks, consisting, respectively, of the remaining 10 items (and lures) from Set A and 10 items (and lures) from Set B. Finally, after approximately 45 min in the recovery room, the patient was administered the fourth recognition task, consisting of the remaining 10 items (and lures) from Set B.

With respect to sedation, this report focuses only on the comparison between baseline and the first PACU test, for which we have the most complete data; these data were analyzed with a repeated-measures analysis of variance (ANOVA) (Table 1). The number of errors on the P-Deletion test went up from baseline to the first PACU retest, ( $F = 4.58$ ;  $df = 1,10$ ;  $p < 0.06$ ); similarly, the number of lines completed on the P-Deletion test decreased ( $F = 5.18$ ;  $df = 1,10$ ;  $p < 0.05$ ); finally, the number of correct responses on the Digit-Symbol Substitution test decreased, ( $F = 5.66$ ;  $df = 1,9$ ;  $p < 0.05$ ). Thus then, overall, the drug did have a significant sedative effect.

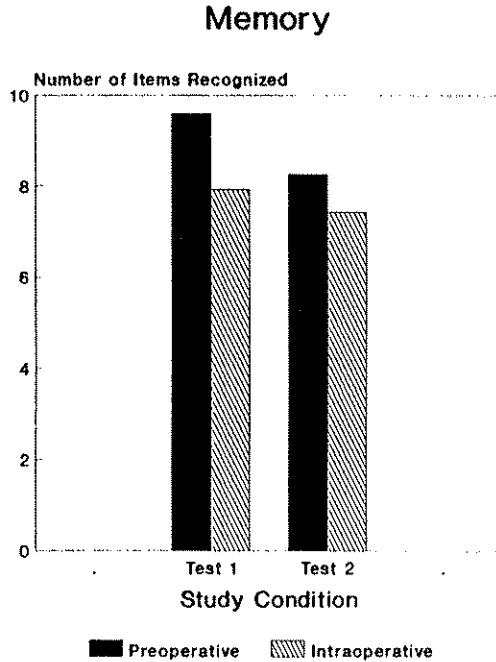
**Table 1.** Performance on Sedation Tests

Variable	Baseline		PACU 15'	
	Mean	SD	Mean	SD
P-Deletion (Errors)	2.18	1.78	3.18	2.14
P-Deletion (Lines)	11.53	5.30	10.09	3.96
Digit-Symbol	28.30	11.98	21.10	13.45

With respect to memory, Figure 1 shows the basic results. A 2x2x2 repeated-measures ANOVA (Study [pre- or intraoperative], by Tests, [first or second] by Item [targets or lures] showed a significant main effect of Item ( $F = 339.20$ ;  $df = 1,11$ ;  $p < 0.0001$ ), indicating that the patients were quite good at discriminating between targets (overall  $M = 8.29$ ) and lures ( $M = 1.27$ ). There were also significant main effects of Study ( $F = 4.55$ ;  $df = 1,11$   $p < 0.050$ , indicating that items studied before surgery were better remembered than those studied while the operation was in progress ( $M = 8.92$  and  $7.67$ , respectively), and Test, ( $F = 6.06$ ;  $df = 1,11$ ;  $p < 0.05$ ), indicating that memory was better on the first test than the second ( $M = 8.75$  and  $7.83$ , respectively). These last two main effects were qualified by a significant Item x Test interaction ( $F = 11.85$ ;  $df = 1,11$ ;  $p < 0.01$ ), implying that the drop between tests was greater for the

list studied preoperatively, than for the list studied intraoperatively (see Figure 1).

**Figure 1.**



N - 12

## **DISCUSSION**

Although mirfentanil appears to have significant sedative as well as analgesic properties, it appears clear that recognition memory for pictures of familiar objects is largely unaffected by the drug. There was no evidence of drug-induced retrograde amnesia: in fact, memory for the list presented preoperatively was better during sedation than afterwards. Moreover, while there was some evidence of anterograde amnesia, in that memory for the intraoperative list was significantly worse than that for the preoperative list, the impairment was very small and may have reflected distractions in the operating room rather than the effect of the drug per se.

*Sedative and Amnesic Effects of Mirfentanil*

Further study of nonpatient volunteers will help to resolve this question. Future research should assess the degree to which these results can be generalized to other aspects of memory and cognition.

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