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# Scopolamine Induced Learning Failures in Man

RONALD C. PETERSEN*

Biomedical Laboratory, Edgewood Arsenal, Aberdeen Proving Ground, Maryland 21010, U.S.A.

*Abstract.* Two experiments were performed to determine the locus of the amnestic effects of scopolamine in man. The first experiment involved 24 volunteers receiving one of three doses of scopolamine (5, 8 or 10 μg/kg) or a placebo, intravenously. The subjects were tested for retention of material learned prior to administration of the drug, acquisition of new information, and retention of material learned while under the influence of the drug. Results indicated that scopolamine has its primary effect on the acquisition of new material and less of an effect on the retrieval of information already learned. The second experiment was designed to refine and expand upon the results of the first and involved 18 volunteers receiving either 5 or 10 μg/kg of scopolamine or a placebo, intravenously. The subjects were given four trials to learn a list of verbal materials, and their recall for that material was measured at various intervals up to 24 h. These results confirmed those of the first experiment in that the predominant influence of the drug was to impair the acquisition of new information. Implications of these results for memory mechanisms are discussed.

*Key words:* Scopolamine – Human learning – Memory – Storage – Retrieval.

Scopolamine is an extremely popular drug used commonly as a component in preanesthetic medication as well as for its sedating, tranquilizing and amnestic properties in situations such as labor, delirium tremens, toxic psychoses and maniacal states (Innes and Nickerson, 1975). Scopolamine or atropine, another belladonna alkaloid, is contained in more than 600 pharmaceutical preparations (Greenblatt and Shader, 1973). The amnestic effect of scopolamine is well known, yet few carefully controlled studies have been performed to document the specific nature of the memory impairment.

While several studies have been conducted to determine the effects of a single dose of scopolamine on a specific aspect of memory, no single study has been performed to investigate several doses of the drug on multiple learning tasks. For example, Hardy and Wakely (1962), in a study designed to investigate scopolamine's amnestic effects at standard therapeutic doses, showed that while the drug did produce some memory loss for line drawings, these deficits were not as severe as one would expect based on anecdotal reports. Hrbek and his colleagues (Hrbek et al., 1971 a, b) showed an impairment in memory for tactile, optical, acoustic and verbal associations using a single dose of scopolamine, while Ostfeld and Arguete (1962) found an impairment on several of the subtests of the Wechsler Memory Scale but not on digit recall. Frumin et al. (1969) did not find any deficit in picture recognition performance over a 24-h period.

Safer and Allen (1971) report that the primary effect of scopolamine on memory appears to be due to a diminished capacity to store new information, while one's ability to recall material immediately remains intact. These conclusions were reached using a digit recall task and a single dose of the drug (10 μg/kg intravenously). The authors cite unpublished work in which they found little impairment in long term memory for verbal materials learned prior to the administration of the drug.

Drachman and Leavitt (1974) in a comprehensive discussion of memory and the cholinergic system found that scopolamine did not impair immediate memory but did affect information storage. In addition, the drug did not interfere with the subjects'

* *Present address:* Mayo Medical School, Rochester, Minnesota 55901, U.S.A.

verbal IQ on the WAIS but did affect their performance IQ. Finally, Ghoneim and Mewaldt (1975) using one dose of scopolamine (8 μg/kg) administered intramuscularly showed that the drug appears to affect information acquisition and, to a lesser extent, recall of previously learned material. Scopolamine also appeared to interfere with certain organizational processes.

Taken together, these studies indicate that scopolamine does have an amnestic effect, yet the precise nature of this effect and the range of doses which produce it have not been specified. These studies used only a single dose of the drug and involved various routes of administration.

The present study was designed to investigate the nature of scopolamine's effect on memory over several doses in the therapeutic range using single and multiple trial learning tasks and measuring recall at various time intervals. By using different but related tasks, it becomes possible to further delineate the locus of these memory deficits. The first experiment used a design similar to that employed by Darley et al. (1973) and Ghoneim and Mewaldt (1975) to assess the drug's effects on storage and retrieval processes. Three doses and a placebo were used. The second experiment was designed to generalize and expand upon the results of the first by examining the effect of the drug on the acquisition of new information using a different task and also by measuring retention of that material over a period of several hours. Two dose groups plus a placebo group were used in this experiment.

## EXPERIMENT I

### *Method*

*Subjects.* Twenty-four male US Army Medical Volunteers ranging in age from 19–28 years with a mean age of 22.90 years and a standard deviation of 2.96 years served as subjects[1]. The mean score on the Army general intelligence test for the subjects was 120.45 with a standard deviation of 12.93.

*Materials.* Two sets of 10 lists of words were selected from Paivio et al. (1968) to serve as the materials to be learned. Each list consisted of 20 high frequency nouns such that four of the nouns were of A to AA frequency, and the remaining words were of frequency of greater than one per million as determined by Thorndike and Lorge (1944). The order of the words in each list was random.

*Drug and Design.* Scopolamine was administered intravenously in one of three doses: 5 μg/kg, 8 μg/kg or 10 μg/kg to a group of six subjects. The fourth group of subjects received a placebo of 2 ml of saline intravenously.

[1] The volunteers in these tests are enlisted US Army personnel who have been given thorough medical and psychological evaluations. These tests are governed by the principles, policies, and rules for medical volunteers as established by AR 70-25 and the Declaration of Helsinki

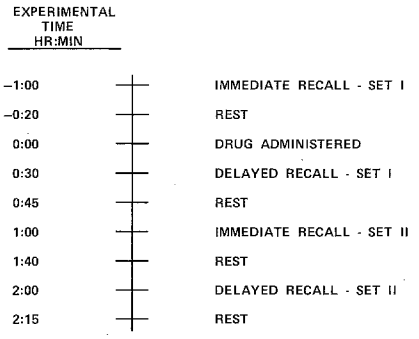


Fig. 1. Testing protocol for Experiment I

A completely randomized design was used with the between-subjects factor being dosage: 5, 8, 10 μg/kg or placebo. Four dependent measures were taken on each subject: a total learning score for the acquisition of the first set of 10 lists, a total delayed recall score for the first 10 lists, a total learning score for the acquisition of the second set of 10 lists and a delayed recall score for the second set of 10 lists.

*Procedure.* The 24 subjects were tested in groups of four with subjects from each experimental group being included in each test session. The subjects were treated identically with exception of the actual dose they received. The testing protocol is shown in Figure 1. At the beginning of the experiment all subjects were presented 10 lists of words for free recall (Set I). The 20 words in each list were read at a rate of one word every 3 s, and following the last word on each list, the subjects were allowed 3 min to produce written recall of the words from that list in any order. The entire learning/recall cycle for the 10 lists took approximately 40 min.

Twenty minutes after the recall of the tenth list in Set I was completed, the drug was administered. The subjects, who had previously been randomly assigned to an experimental treatment group, were given their appropriate dose of the drug or placebo. Previous work (Ketchum et al., 1973) involving the administration of scopolamine intravenously has indicated that cognitive functions are approaching their maximum level of depression by 30–45 min after dose. Therefore, the subjects were then allowed to rest for 30 min. Following the rest period, the subjects were tested for delayed total recall of the words from the 10 lists in Set I. The subjects were instructed to free recall the words from any of the lists and were allowed 15 min to complete this task.

At the conclusion of the delayed recall task, the subjects rested for 15 min and were given Set II consisting of 10 new lists of 20 words each. The subjects were instructed to learn each list and recall it immediately using a procedure identical to that used with Set I. This learning/recall procedure lasted approximately 40 min. Twenty minutes after the completion of the immediate recall task, delayed recall of all of the items in Set II was measured. The subjects were allowed 15 min to complete this task. The entire testing procedure took approximately 3 h 15 min with the last 2 h 15 min of the test being conducted under the influence of the drug.

### *Results*

The immediate and delayed recall means for each of the four groups on both sets of lists appear in Table 1. A one-way analysis of variance was performed on each of the four measures taken on the subjects with the single factor being the dose condition.

Table 1. Recall means (standard deviations in parentheses)

| Groups | Total immediate recall set I | Delayed recall set I | Total immediate recall set II | Delayed recall set II | Delayed recall as percentage of immediate recall set II[a] |
|---|---|---|---|---|---|
| Placebo | 77.83 (18.38) | 26.83 (13.79) | 82.33 (19.23) | 37.00 (21.88) | 42.08 (16.99) |
| 5 μg/kg | 77.67 (5.32) | 29.83 (10.87) | 35.33 (4.76) | 8.50 (5.61) | 23.11 (13.33) |
| 8 μg/kg | 73.00 (13.07) | 25.33 (6.59) | 25.50 (8.62) | 4.67 (2.34) | 19.04 (8.63) |
| 10 μg/kg | 76.67 (8.38) | 21.83 (7.36) | 18.50 (4.09) | 1.83 (2.23) | 9.03 (10.68) |

[a] These figures represent the mean of the individual subject percentages within each group

The learning score for the immediate recall of Set I was derived by summing the individual recall scores for each of the 10 lists in the set. This measure served as an index of how much information the subject had acquired during the entire learning phase. The analysis of variance on this measure revealed no differences among the four groups [$F(3,20) = 0.20$, $P > 0.05$]. Inspection of the means in Table 1 indicates that all four groups learned an equivalent amount of information which is what one would expect, since, at this point, no drug had been administered. The equivalence of the groups also supports the contention that the four groups were approximately equal in terms of sampling of subjects; that is, all groups appeared equal in their ability to learn.

An analysis of variance similarly did not reveal any differences among the four groups on the delayed recall of the words from Set I [$F(3,20) = 0.65$, $P > 0.05$]. Inspection of the delayed recall means in Table 1 indicates that the drug did not appear to impair retrieval processes at this recall interval. Apparently once the material had been stored, the subjects were able to recall it in spite of the influence of the drug.

The drug did have a substantial effect on the subjects' ability to learn new material. The analysis of variance on the total learning score for the 10 lists in Set II revealed a significant main effect due to dose [$F(3,20) = 44.61$, $P < 0.001$]. Scheffé contrasts on the group means indicated that the three drug conditions recalled significantly fewer items than did the placebo condition ($P < 0.05$), but the three drug groups did not differ among themselves.

To assess the effect of various doses of the drug on the delayed recall of Set II, a percentage measure was calculated. Whereas Ghoneim and Mewaldt (1975) performed their analysis on the absolute number of items recalled in the delayed recall test, it was felt that a measure which reflected the level of original learning of the material would be more appropriate. Since the subjects learned different amounts of material as a function of their dose group (significant dose effect on learning scores for Set II), this should be taken into account when developing a retrieval measure. A percentage of initial amount learned appeared more appropriate since one could now assess recall independently of the level of original learning. An arcsin transform (Myers, 1972) was performed on these data before they were submitted to an analysis of variance. The analysis revealed that the groups differed in the percent they recalled [$F(3,20) = 6.56$, $P < 0.01$]. Scheffé contrasts on the mean percentage indicated that the mean of the three drug groups did not differ from the placebo condition nor did the three drug groups differ among themselves ($P > 0.05$). The only significant difference among the groups was due to the 10 μg/kg group which differed significantly from the placebo condition ($P < 0.05$). With this being the only significant effect, it appears that scopolamine does not greatly affect retrieval processes, except perhaps at high doses.

### *Discussion*

The results of this experiment appear to indicate that the primary locus of scopolamine's effect on human memory resides in the acquisition of new information. The drug did not impair the recall of information stored prior to administration of the drug (Set I) and only minimally impaired the recall of material stored in the drug state (Set II). All three doses of the drug did impair the learning of new material as was indicated by the acquisition data from Set II. The 5 μg/kg dose was sufficient to cause an impairment in new learning, and while the 8 μg/kg and 10 μg/kg groups performed below the 5 μg/kg group, the differences were not statistically significant. Analysis of the individual learning trial protocols of the subjects revealed that most of the subjects in the drug conditions were recalling primarily the last few items on each list, and one could not be certain that the subjects were attending to the entire list. That is, one of the

problems in using scopolamine and this type of task is that the subjects have a difficult time maintaining their attention on the task. Therefore, to assess the generalizability of these results, a second experiment was designed to ask a similar set of questions as the first experiment using a different experimental task.

## EXPERIMENT II

This experiment was designed to determine if scopolamine influences information acquisition and retrieval when the subjects are required to process, at least minimally, all of the input materials. Two of the doses, 5 and 10 µg/kg, used in Experiment I and a placebo were used. The 8 µg/kg condition was omitted because on the basis of the results in Experiment I, it did not appear to be substantially different from the 10 µg/kg dose.

The subjects were once again required to recall lists of words, yet the task differed from that of Experiment I in two significant respects: (1) The subjects were required to make a response after each word on the list to ensure they at least were attending to the material, and (2) they were required to perform a brief arithmetical task between hearing the last item on the list and beginning recall. This procedure reduced the likelihood of subjects recalling only the last few items on the list just because they were the last items on the list. In other words, this procedure minimizes the role of short-term memory in this task. These two manipulations allowed a more definitive assessment of the basic memory mechanism issues raised in Experiment I.

### *Method*

*Subjects.* Eighteen male US Army Medical Volunteers ranging in age from 18–31 years with a mean age of 21.28 years and a standard deviation of 3.39 years served as subjects[1]. The mean Army general intelligence score for the subjects was 114.31 with a standard deviation of 14.49.

*Materials.* One list of 20 high frequency nouns was selected from Paivio et al. (1968) as the materials to be learned. The words were selected such that all were of A or AA frequency, and all were concrete nouns. Each subject was given four sheets of paper with 20 lines of four words typed on each. One of the four words on each line was one of the four words on the list, and the other three items were randomly selected from Paivio et al. (1968). The sequence of the 20 target words on each sheet corresponded to the order in which the words would be read. There were four corresponding sheets.

*Drug and Design.* Scopolamine was administered intravenously in either a 5 or 10 µg/kg dose to six subjects. Another group of six subjects received a placebo of 2 ml of saline intravenously.

The experiment was divided into two phases, an acquisition phase and a delayed recall phase. During the acquisition phase, four learning measures were taken on each subject, and during the delayed recall phase, six retention measures were taken. A mixed design was used for each phase of the experiment. For the acquisition phase the between-subjects factor was dosage (5, 10 µg/kg or placebo), and the four learning trials constituted the within-subjects factor. For the delayed recall phase, the between-subjects factor was, once again, dosage and the within-subjects factor involved the six recall tests.

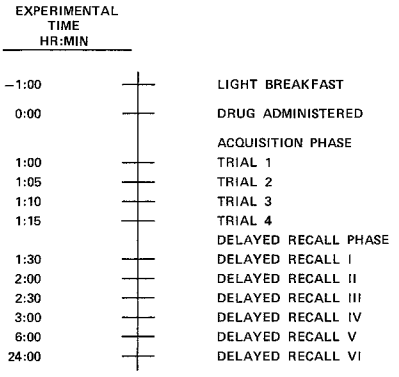


Fig. 2. Testing protocol for Experiment II

*Procedure.* The 18 subjects were tested in groups of six with subjects from each of the three experimental groups being included in each test session. All subjects were treated identically with the exception of the actual dose they received. The testing protocol is shown in Figure 2.

Following a light breakfast, the subjects were administered their appropriate doses. Sixty minutes after the dose, the subjects were read the list of 20 words at a rate of one word every 3 s. As each word was read the subjects were to circle the word from among the four which appeared on the appropriate line on their sheets. This constituted a multiple-choice type of exercise which ensured that each subject was attending to the task and processing each word. Following the last item on the list, the subjects engaged in a 1-min subtraction task. Then they were instructed to recall as many items from the list as possible in any order and were allowed 3 min to complete this. This learning procedure was repeated three more times, using a different random sequence on each trial, yielding a total of four acquisition trials.

Ten minutes after the last list and at half hour intervals after that up to 1.5 h, delayed recall tests were given. Finally, two additional delayed tests were given at 6 and 24 h after dose. Subjects were allowed 3 min for each of these tests.

### *Results*

A two-way analysis of variance with one between-subjects variable (dose) and one within-subjects variable (trials) was performed on the acquisition phase of the experiment and another on the delayed recall phase. The means for the two phases of the experiment are plotted in Figure 3.

The analysis of variance on the acquisition phase revealed a significant main effect due to dose [$F(2,15) = 17.34$, $P < 0.001$). Contrasts on the dose means indicated that the placebo group learned more than the 5 µg/kg group which learned more than the 10 µg/kg group ($P < 0.05$). Contrasts on the trial means indi-

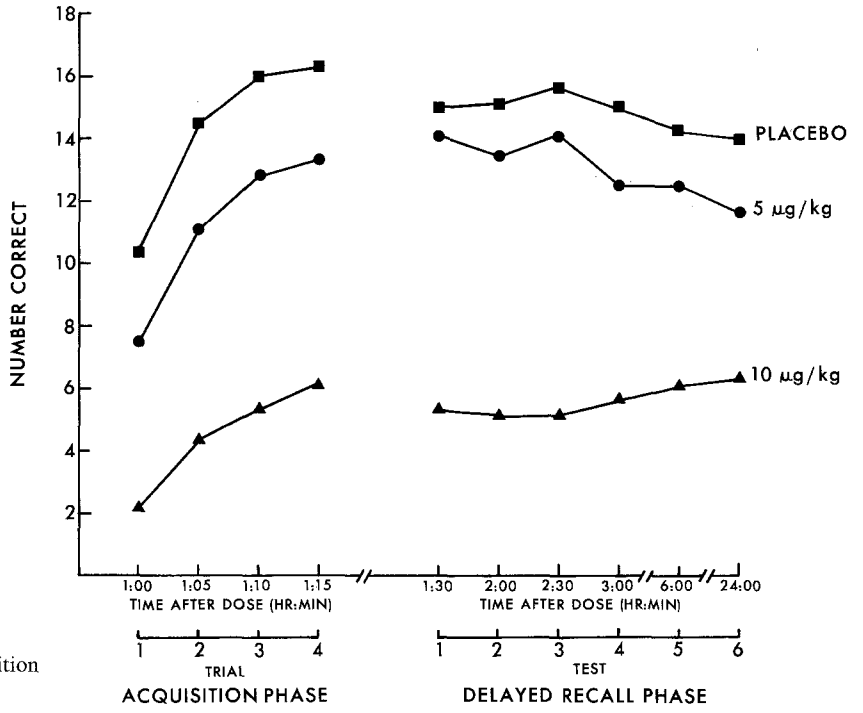


Fig. 3. Group recall means during the acquisition and delayed recall phases of Experiment II

Table 2. Mean difference scores (standard deviations in parentheses)

| Group | Delayed recall test | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| Placebo | − 1.67 (1.50) | − 1.50 (1.38) | − 1.00 (2.00) | − 1.67 (1.03) | − 2.33 (1.51) | − 2.67 (2.42) |
| 5 µg/kg | 0.17 (2.48) | − 0.50 (2.59) | 0.17 (1.94) | − 1.50 (1.76) | − 1.50 (2.34) | − 2.33 (1.63) |
| 10 µg/kg | − 1.17 (2.14) | − 1.33 (2.34) | − 1.33 (2.86) | − 0.83 (2.48) | − 0.33 (1.38) | − 0.17 (2.10) |

cated that the subjects learned more words on each successive trial through Trial 3 ($P < 0.05$). On Trial 4 there was once again an increase in performance, but the increase was not statistically significant. This is evident from Figure 3 in that the three learning curves increase over the first three trials and level off at the fourth trial. It should also be noted that the three learning curves are essentially parallel which is consistent with the nonsignificant dose by trials interaction term. Apparently the drug influences the amount of material one can learn rather than the rate of learning.

Figure 3 also displays the recall means on the delayed recall tests. To investigate the effects of the drug on recall processes independently of initial acquisition, a difference score was calculated for each subject. The difference was taken between the number of items each subject recalled on each delayed recall test and his highest score during the four acquisition trials. This measure served as an index of the amount of material forgotten. The group means for this measure appear in Table 2. These difference scores were submitted to a two-way analysis of variance (dose by recall test) which revealed a significant effect due to recall test [$F(5,75) = 4.69$, $P < 0.01$]. Scheffé contrasts on the recall test means indicated that significantly more items were remembered on Recall Test 1 than on Test 6 ($P < 0.05$), with the difference between Test 1 and Test 5 approaching significance. These results demonstrate that the subjects did not forget an appreciable amount of material over the half hour tests up to 3 h. However, they began to demonstrate some forgetting by the 6-h test and a significant amount by the 24-h test. The nonsignificant dose by recall test interaction indicates that this pattern was essentially true for all groups, and in particular, that scopolamine did not affect this process to any great extent since the two drug groups were not different from the placebo.

The results of the delayed recall phase of the experiment should be interpreted with some caution since a multiple recall testing procedure was used.

The subjects were not presented with the material during the recall tests, nor were they informed of their performance; however, the act of recalling the material may have served as a type of study trial which could have resulted in spuriously high recall curves. While this does not negate the results, especially at the 6 and 24 h recall intervals, this procedure should be kept in mind when interpreting the recall curves.

*Discussion*

The results of this experiment confirm those of Experiment I. Scopolamine had a significant influence on the acquisition of new information as was evidenced by the main effect of dose during the four learning trials. The placebo group learned more material than did the 5 μg/kg group which in turn learned more than the 10 μg/kg group. When the groups were adjusted for the degree of initial learning, however, the drug appeared to have little effect on subsequent recall as was shown by the nonsignificant dose effect during delayed recall. All three groups appeared to forget about the same amount of material over the 24 h recall period.

## GENERAL DISCUSSION

The results of the two experiments were quite consistent in that they both indicated that scopolamine primarily influences a person's ability to acquire new information and only minimally impairs one's ability to retrieve information once it has been stored. The two experiments used different but related tasks to demonstrate these findings. The first experiment showed that the drug had no effect on recall of material learned prior to the administration of the drug. It also showed that the drug had a profound effect on the acquisition of new material but little effect on the recall of the material once it had been learned. The second experiment revised the task to yield more information concerning the effects of the drug on acquisition and retention processes and confirmed the results of the first experiment. Using a multiple-trial acquisition task, scopolamine was, once again, found to have a marked effect on the subject's ability to learn the new material. However, once the material had been learned, it was retained equally well for all subjects up to a 24 h interval.

These results are consistent with Safer and Allen (1971) and Ghoneim and Mewaldt (1975). The present study using several doses and two tasks expands upon the speculations offered in these studies. Both Safer and Allen (1971) and Ghoneim and Mewaldt (1975) used single doses of the drug and gave recall tests after a single exposure to the material to be learned. The present study used several doses and tasks which involved both single and multiple exposures to the material to be learned.

It may be that drugs such as scopolamine interfere with the acquisition of new information by impairing attentional processes. The subjects in these experiments appeared to have had a good deal of difficulty concentrating on the task, yet they were well motivated and were putting forth an effort. They reported the tendency for their minds to wander, and their attention spans were short. This was part of the rationale for changing the task in Experiment II to require the subjects to respond after each word on the list to ensure that they had at least processed the items minimally. When this procedure was followed, however, the effect of the drug on acquisition remained; so, to the extent this procedure compensated for attention lapses, the contribution of impaired attention to the acquisition deficits appears minimal.

Ghoneim and Mewaldt (1975) felt that the drug may have been influencing the transfer of information from short to long-term memory. They found no effect of the drug on immediate recall nor any effect on information learned prior to the administration of the drug. They did find an effect on the acquisition of new information and felt that this must have been due to interference with the storage process itself. This is plausible, and the present study supports this argument. This reasoning is consistent with work demonstrating deficits in transfer of information from short to long-term memory in patients with lesions in the hippocampal region (Drachman and Arbit, 1966; Drachman and Ommaya, 1964; Milner, 1967; Penfield and Milner, 1958; Scoville and Milner, 1957). Since the hippocampal region is a well known cholinergic area (Drachman and Leavitt, 1974) and scopolamine is an anticholinergic drug, this type of memory deficit would not be unreasonable. However, these arguments are speculative since the notion of short and long-term memory espoused in various memory models (Atkinson and Shiffrin, 1968; Kintsch, 1970) is an hypothetical construct and the correspondence between these models and physiological data is, at best, tenuous.

Nevertheless, the fact remains that scopolamine affects acquisition processes to a greater extent than retrieval processes. More research needs to be done in man to elucidate just how this drug affects these processes and cognition in general.

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