THE AMNESIC EFFECT OF DIAZEPAM (VALIUM)

BY

P. R. F. CLARKE, P. S. ECCERSLEY, J. P. FRISBY AND J. A. THORNTON

SUMMARY

A double-blind trial of intravenous diazepam (0.24 mg/kg) versus saline was carried out on twelve young intelligent male volunteers to examine the amnesic effect of the drug. Complex psychological testing extended over a 2-hour period. Dense anterograde amnesia was found for approximately 10 minutes with a less severe impairment of memory persisting at least half an hour after injection. It is considered that the memory difficulties were not due to serious reduction of level of consciousness but do focus on the input or “consolidation” processes rather than on retrieval. Further studies are needed to define more clearly the nature of the deficit.

The present study arose from the clinical observation of amnesia following the use of intravenous diazepam in oral surgery and dental conservation. Many authors have noted such an effect and several have studied it in clinical series. Recent examples include Brown and Dundee (1968), Fox, Wyans and Bhamhahi (1968), Frumin, Herekar and Jarvik (1969), and O'Neil and Verrill (1969). In general the amnesic effect has been considered a valuable bonus and exploited to cover a variety of unpleasant and anxiety-provoking procedures. An outline of the pharmacology of diazepam and of its uses in anaesthesia can be found in Knight and Burgess (1968).

The phenomenon of postoperative anterograde amnesia has frequently been reported and related variously to premedication technique (Feldman, 1963) or general anaesthesia (Fox, Wyans and Bhamhahi, 1968; Gruber and Reed, 1968). Hardy and Wakely (1962) writing on hyoscine and atropine consider that the mechanism involved is analogous to light general anaesthesia causing “central depression” which attacks memory storage as the most vulnerable function. Mazzia and Randt (1966) in an elegant demonstration implicate the arousal system in both anaesthesia and pathological memory disorders. Since Parkes (1968) considers that diazepam acts to suppress stimulation of the hippocampus via the amygdala in the cat, it is tempting to relate the clinical findings to specific disorders of memory of the sort described by Scoville and Milner (1957) and Penfield and Milner (1958) in bilateral hippocampal damage. The complexities of measuring amnesia have been brought out by several authors, e.g. Gruber and Reed (1968), Milner (1968), Whitty and Zangwill (1966), and Deutsch (1969).

In order to clarify some of these points it was decided to use diazepam alone in an experimental setting, to ensure that the subject was awake when the information was put in, and to measure a number of different complex cognitive functions.

PROCEDURE

In order to reduce the individual differences as much as possible, twelve young intelligent male volunteers served as subjects (ten dental students, a research physiologist, ages 20–23, and a senior medical technician, age 34). They were assigned to the experimental or placebo group by the


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anaesthetist according to a random number table prepared by one of us who did not see the subjects himself. The anaesthetist alone knew which treatment the subject received but he was not involved in any subjective assessment procedures: the other experimenters were kept in ignorance of the treatment except that the behavioural changes were so marked that there was rarely any doubt about it.

The time course of the initial procedure is set out in figure 1. The subjects were brought fasting to the laboratory where the anaesthetist made a brief medical inquiry and examination. As they lay reclining on a couch, a technician gave them a decision-making task, a practice run on a vigilance task and a list of words to remember (on tape). The anaesthetist then administered intravenously either saline (1 ml/min) or undiluted diazepam (0.24 mg/kg at a rate of 5 mg/min). Thus the injection lasted 3–4 minutes: 2 minutes before it was completed the vigilance test began. This task was interrupted at equally spaced intervals by three more lists of words to remember (on tape). The anaesthetist then administered intravenously either saline (1 ml/min) or undiluted diazepam (0.24 mg/kg at a rate of 5 mg/min). Thus the injection lasted 3–4 minutes: 2 minutes before it was completed the vigilance test began. 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of wrong answers, and the number of times the sum was mistakenly given instead of the word “Repeat”.

Memory lists. Lists of 8 words in each of four categories (animals, parts of the body, vegetables, birds) were constructed like those of Bousfield (1953) but selected to be appropriate to a British population. Each list was equated for frequency of occurrence in the English language (Thorndike and Lorge, 1944): only one word occurs 40–49 times per million, one 30–39 times, one 20–29 times, one 10–19 times, and four between 2 and 9 times. They are thus relatively infrequent words but care was taken not to include subjectively “difficult” words. The 8 words were interleaved and repeated 3, 4 or 5 times to form a complex list of 30 items recorded on tape at approximately 1 every second. The subject’s task was to listen to and remember the 8 words used in each list. His scores were the number of lists he thought he had heard, the number of words within each list that he recalled and the number of words he could correctly select from recognition sets of 16 words, containing 8 equally frequent “confusion” items which had not been previously presented.

Triple-associate learning test. This test was devised by one of the authors for the assessment of various memory difficulties in neurological and psychiatric patients. It was reported orally by Clarke in 1960 and has been used clinically since but as yet has no standardization data. The subject is asked to try to remember 6 sets of 3 words which are read aloud as 6 triplets, the 3 words in a triplet having a phonic similarity (see table I).

His learning is tested by prompting him with the first (stimulus) word of each triplet and asking for the other 2 words which went with it.

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tbody>
<tr>
<td><strong>Triple associate learning materials (Set I)</strong>. The stimulus word in each set is underlined; the subject has to learn to respond with the other two words.</td>
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<tr>
<td>cur</td>
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<tr>
<td>tape</td>
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<tr>
<td>thrust</td>
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<tr>
<td>win</td>
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<td>dodge</td>
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<td>pick</td>
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He is corrected at once if he gets them wrong and the whole list of triplets is tried 4 times. This provides a measure of immediate memory (number of response words correct after the first hearing), and 2 measures of learning (number correct summed over 4 trials, and the number which are correct 3 times in a row in these 4 trials). Obviously, in order to measure retention, it is necessary to make sure that material has been adequately learned, and so, where necessary, further trials are given of one or two triplets until at least 4 items have been correct 3 times consecutively. After a “forgetting period” of half an hour, retention is measured in 3 different ways. First the subject is asked to recall as many of the 18 words as he can without regard to order or grouping (free recall). Next he is prompted with the first word of each triplet and is asked to respond with the correct words as in the original learning except that his answers are not corrected (prompt recall). Finally, a list of 21 words is read to him and he is asked to select the 12 which were the response words of the triplets originally learnt (recognition).*

Intelligence tests. These were chosen to test a range of different intellectual functions in a brief period. One was a shortened 10-item version* of the synonym-selection form of the Mill Hill Vocabulary (Raven, 1958) to provide a measure of word knowledge relatively insensitive to temporary intellectual inefficiency. This was given on both occasions. The other tests were taken from the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955) on the first occasion and from the Wechsler Bellevue Form II (WB II) (Wechsler, 1946) on the second. These are standard American tests of general intelligence administered individually and are designed to be parallel forms for repeated testing. Each consists of a number of subtests of which only two were given here, the Similarities and the Block Designs. Both of these are relatively sensitive to intellectual impairment even on a temporary basis. The Similarities involves explaining how two named things are alike and might be taken as a measure of verbal skill relevant to word learning. The Block Designs

* Fuller details of these tests may be obtained from P. R. F. Clarke.
AMNESIC EFFECT OF DIAZEPAM (VALIUM) involves copying patterns with wooden cubes and measures more spatial aspects of intelligence: as the only timed test given it was expected to be specially sensitive to impairment.

RESULTS

Level of consciousness and general intellectual efficiency.

The clinical observation of amnesia after diazepam might be due to a specific disruption of storage and retrieval processes or instead it might reflect general intellectual impairment or simply loss of consciousness.

There was clear evidence that the experimental subjects were less efficient on the vigilance task than the controls but it was equally clear that they were not asleep or unconscious (see fig. 2). Errors were few in both groups. All the experimental group but only 2 of the 6 control subjects made errors (Fisher test, \( P<0.025 \) one-tail; Siegel, 1956). Omissions were rare: only 2 errors were made, both by experimental subjects. Only 2 experimental subjects gave a substantial number of wrong answers, but the occasional “repeat” task showed more consistent differences suggesting that the bridging of the 5-second gap between digits was difficult for the experimental subjects. Thus while there is evidence that the experimental subjects were clearly awake they nevertheless showed some impairment of intellectual function. This view is supported by the finding that 5 of the 6 diazepam subjects showed slurring of speech during the task while none of the controls did.

Diazepam marginally affected the decision-making task. This was shown by an analysis of variance of “difference scores” calculated for each of the three measures by comparing pre- and post-injection readings, a procedure which enabled each subject to act as his own control. A full discussion of the findings that resulted will be presented elsewhere (Frisby et al., in preparation). For the present it will simply be noted that the two groups of subjects did not differ significantly on either their “accuracy” or on their “number of cards required” difference scores, but that they did so on their “confidence rating” results. Thus, for the most “difficult” packs (these had means actually equal to the criterion of 74), the diazepam group lost confidence in their decisions following injection, whereas the saline group showed a corresponding gain in confidence on the later administrations of the task (\( P<0.05 \)).

No significant differences could be demonstrated between the two groups on the three intelligence tests used. Table II shows that the groups were above average intelligence on the two Wechsler subtests on both occasions although there were some surprisingly low scores for such a sample.

Similar figures are not available for the abbreviated version of the vocabulary test used; these scores clustered at a level approximating the top end of the average range for Raven’s (1958) norms.

In summary then, there is evidence of only slight reduction in level of consciousness with this dose of diazepam and ample evidence that short-term processing of input is accurate even

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<td>Intelligence test scores. WAIS scaled scores at the experimental session; WB II weighted scores at follow-up. (These scores have a mean = 10 and SD = 3.)</td>
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<tr>
<td><strong>Test day</strong></td>
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<td></td>
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<tr>
<td><strong>Similarities</strong></td>
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<td>Median</td>
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<td>Range</td>
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<td><strong>Block designs</strong></td>
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<td>Median</td>
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Vigilance task errors (raw scores). Vertical axis represents number of subjects in each group obtaining each of the scores along the horizontal axis in response to a total of 121 digits including 11 repeats.
during the peak period of the dose. There is also good evidence of normal complex processing within an hour or even within 20 minutes of the injection.

Memory.

The retention tests for the word lists provide measures of storage of material put in during the first few minutes after the injection. The triple-associate tests offer evidence of what aspects of memory are most affected approximately half an hour after the injection at a time when the subjects looked and sounded almost normal, just after performing well on the decision-making task and just before intelligence tests showed no general intellectual impairment.

Figure 3 presents the frequency distributions of the raw scores for the memory lists. List A (animals) served as an index that both groups could retain this type of information over a period of about 100 minutes because it was presented before the injection. Both groups recalled and recognized the names of the animals well and no significant difference could be demonstrated between them. Incidentally, this finding represents some evidence against the development of retrograde amnesia in the present study. Lists X, Y and Z, presented after the injection, revealed that diazepam does indeed have an amnesic effect. The experimental group were significantly worse than the controls in recalling all three lists (Mann-Whitney U (Siegel, 1956): list X, P=0.001; list Y, P<0.002; list Z, P<0.002). The differences in recognition were also significant (P=0.001, P=0.001 and P<0.02 respectively). Thus the material appears inaccessible to both recall and recognition although it may be presumed to have been perceived since the vigilance task was not seriously impaired. There is a hint that the memory deficit was already receding after 10 minutes since the experimental group succeeded in retrieving some of list Z. It is worth remarking that while all the controls recalled the categories used in at least three of the lists, only one diazepam subject recalled that he had heard more than the single list of animals (Mann-Whitney U, P<0.004).

Figure 4 presents the median learning curves for both groups at test and at follow-up on the triple-associates. The immediate recall scores on this test were not significantly different under saline or diazepam, which supports the evidence

![Graph](image-url)
AMNESIC EFFECT OF DIAZEPAM (VALIUM)

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FIG. 4
Triple-associate learning: median learning curves for both groups at the experimental session (set I words) and the follow-up session (set II words). Maximum possible score 12 (vertical axis) on each of the four trials (horizontal axis).

from the decision-making task and the intelligence tests that general intellectual efficiency was not much reduced in the period 15–50 minutes after the injection. The two measures of learning, however, showed the experimental subjects to be clearly inferior. Total correct responses in four trials showed very little overlap (P = 0.002) and the number of items reaching criterion in four trials showed no overlap (P = 0.001, Mann-Whitney U). However, once stored the material appears to be normally accessible. On none of the three retention measures were the diazepam subjects different from the controls for the words which had met the learning criterion. The controls were, however, better at recalling the items which failed to meet that criterion (Free recall, P = 0.013; Prompt recall, P = 0.032; Recognition, P = 0.09, Mann-Whitney U). Thus there is good evidence of an impairment which is fairly specific to memory and probably particularly involves the input or storing phase rather than retrieval.

Follow-up study.

In order to demonstrate that the observed deficit had disappeared and to assure ourselves that our two groups of subjects had similar memory abilities, a parallel set of triple-associates and the intelligence tests were given after several weeks to both groups (table II and fig. 4). These again yielded 13 scores. Four of these had shown significant impairment under diazepam, but now it was found that the two groups did not differ significantly on any of the measures. Moreover, the controls had not changed significantly on any of the 13 measures while the experimental subjects had improved on the four measures which had demonstrated impairment. This improvement was statistically significant (P = 0.016) for the two learning scores and approached significance (P = 0.062) for the two retention scores for poorly learnt items (Walsh tests; Siegel, 1956).

DISCUSSION

The present findings demonstrate unequivocally that intravenous diazepam at this dose level produces a clinical picture of dense anterograde amnesia at least for about 10 minutes, followed by a period of better but still impaired memory function. The exact nature of these deficits is less clear.

There is no direct evidence that the memory lists were perceived or stored under the influence of diazepam. Although the subjects could carry out the vigilance task fairly accurately it is possible that they may have gone to sleep during the recitation of the lists. This does not seem very likely in that there was no consistent bunching of errors immediately following each list such as might reflect lowering of conscious level. It is useful to point out here that such an explanation could not account for the learning impairment on the triple-associate test. If it is assumed that the memory lists were perceived and briefly stored, then the deficit might be in any of the phases of memory—"consolidation", storage, or retrieval. Since recall is usually a more difficult retrieval task than recognition, the fact that both were more or less equally affected offers some evidence to implicate the consolidation or storage phases.

This conclusion is supported by the difficulty shown in the triplets test half an hour after the injection. At this stage the subjects were clearly conscious and we can be sure that the material was perceived since they had to recall the response words to reach the learning criterion. Subsequently the retrieval tests demonstrate the expected pattern (recall harder than recognition) and show no impairment relative to the saline
group for those items adequately learnt. Nevertheless the learning scores were significantly impaired. Since the measure of learning on each trial was the success of a recall process it might be argued that the deficit was merely in this technique of retrieval over the short term. However, such an explanation would not comfortably account for the subsequent differential retrievability of the "well-learnt" and "poorly-learnt" items which showed up to some extent even in recognition.

It should be pointed out that Frumin, Herekar and Jarvik (1969) came to similar conclusions using pictorial material although it must be remembered that they used diazepam in combination with hyoscine.

It is interesting that the present diazepam subjects show no evidence of retrograde amnesia and may even benefit from the drug in their recall of the memory list. A. Summerfield and Steinberg (1957) concluded that nitrous oxide given after learning may facilitate recall by preventing interference from new input, and Pearlman, Sharpless and Jarvik (1961) consider that a general anaesthetic administered after consolidation is complete will similarly preserve the trace whereas, given beforehand, it may block the consolidation process itself and the trace may be lost.

If it is accepted that the defect did occur in the consolidation stage it is still arguable whether this should be seen as a difficulty specific to memory or as a reflection of more general lowering of intellectual efficiency. The subjects may have shown poor concentration or confusion in general or even a lowered enthusiasm consequent to the tranquilizing and relaxant properties of diazepam. The very slight effect on the decision-making task and the absence of impairment in the immediate memory and intelligence scores (particularly the Block Designs) contraindicates general intellectual impairment. The clinical impression of the psychologist was that motivation was not reduced.

The clinical literature on the amnesic syndrome commonly describes relatively good general intellectual efficiency and immediate memory, although these functions clearly suffer in dementia. On occasion severe specific amnesic states show mainly difficulties in retrieval (Clarke, 1961) although clearly the famous case "H.M." failed to show savings except in a mirror-tracing task (which he could not recognize) (Milner, 1968). It remains to be established whether such specific amnesic syndromes are essentially different from the possibly more generalized anterograde amnesia observed following unconsciousness. However, the deficit observed with diazepam may be an experimental model for either, allowing finer investigation of the clinical phenomena. To carry this work further, more sensitive monitoring of consciousness and better experimental definition of the phases of memory are needed.

ACKNOWLEDGMENTS

We wish to thank Mr. P. Herbert, F.L.M.L.T., chief technician, and Mrs. P. Tatt for their help in carrying out this investigation.

REFERENCES


Prolonged tracheal intubation: the problem of changing the tube: an easy solution

Sir—Prolonged tracheal intubation is commonly used, as an alternative to tracheostomy, in a variety of conditions—coma, respiratory distress—and has gained the favour of many anaesthetists, since it is easily performed, and avoids some of the well-known complications of tracheostomy.

Intubation may be achieved through the oral or the nasal routes, the nasal being favoured by most, since it is more acceptable to a conscious patient, and less likely to lead to complications such as biting on the tube or displacement.

However, whether the tube is introduced through the nose, the mouth or a tracheostomy, it is likely to become obstructed by plugs of mucus, blood or secretions, and therefore has to be removed and replaced by a new one.

The replacement is not always easy, since the patient may be unconscious or in severe respiratory distress, and the procedure has to be carried out as an emergency. Blind nasal intubation is not always successful at the first attempt; laryngoscopy may prove difficult, if not impossible, and may induce trauma. Even in the case of tracheostomy, on a fat, short-necked patient, unless the tube has been in site for some time and the case of tracheostomy, on a fat, short-necked patient, unless the tube has been in site for some time and the tube obstructed by mucus, blood or secretions, and therefore has to be removed and replaced by a new one.

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