Brit. J. Anaesth. (1971), 43, 113

EFFECT OF METHOHEXITONE, DIAZEPAM AND SODIUM 4-HYDROXYBUTYRATE ON SHORT-TERM MEMORY

BY

I. G. GROVE-WHITE AND G. R. KELMAN

SUMMARY

Short-term memory following the intravenous injection of methohexitone (0.15 mg/kg), diazepam (0.05 mg/kg) and sodium 4-hydroxybutyrate (10 mg/kg) has been examined by means of a visually presented digit retention test with intervals of 4 and 20 seconds before recall. No significant change was found with the 4-second interval; statistically significant impairment was found with the 20-second interval. It is postulated that the effect of these drugs is to accelerate decay of the memory trace, thus impairing its consolidation and producing anterograde amnesia. A versatile computerized test of short-term memory is described.

The amnesic effects of drugs have been of value in minor oral surgery for some years. A drug-induced state of amnesia and general analgesia was advocated by Jorgensen and Leffingwell (1953) and there have since been several modifications of their technique. Methohexitone sodium alone can produce a similar state of amnesia and analgesia when given in small incremental dosage (Clarke, 1967). More recently the benzodiazepine tranquillizer diazepam has been used in conjunction with local analgesia; amnesia is a prominent feature of this technique (Brown and Dundee, 1968; Frumin, Herekar and Jarvik, 1969; O'Neill and Verril, 1969).

The present study is an attempt to measure and clarify the effect of these last two drugs on the short-term component of memory. In addition, a third drug, sodium 4-hydroxybutyrate (4-OHB) has been studied. While this is known to produce unconsciousness, amnesia has not been reported following its use.

METHOD

The experimental subjects were ten student volunteers (five male, five female) aged between 19 and 22 years and weighing 55–85 kg.*. They were asked not to smoke or drink alcohol or caffeine-containing beverages either before or during the experimental period.

Testing took place in a windowless room with subdued, but constant ambient light. Each subject was seated before a keyboard (Teletype ASR-33) and the screen of a storage oscilloscope (Tektronix 401) which were both connected "on-line" to a digital computer (Digital Equipment Corporation PDP8/S). The computer was programmed to display strings of random digits or letters on the oscilloscope screen. The subject was required to remember these characters for a predetermined time interval, and then to recall them and type them on the keyboard. The computer checked the correctness of the subject's responses.

TABLE I

Mean numbers of errors made by each subject in pre-injection tests.

Subject	Number of errors	
	4-second interval	20-second interval
1	1.3	2.6
2	0.1	0.5
3	0.8	1.3
4	0.3	2.0
5	6.3	9.8
6	13.8	21.3
7	7.9	9.9
8	4.0	12.0
9	3.0	6.3
10	9.6	10.4
Mean	4.7	7.6
SD	4.6	6.4

* See table I of our previous paper on page 110.

I. G. GROVE-WHITE, M.B., F.F.A.R.C.S., Departments of Physiology, University of Aberdeen, and Anaesthetics, Aberdeen Royal Infirmary; G. R. KELMAN, M.D., M.SC., PH.D., D.I.C., Department of Physiology, University of Aberdeen, Scotland.

The test procedure was initiated by the subject in his own time. Three seconds later a 6-digit number was displayed in the centre of the oscilloscope screen, where it remained for 6 seconds, and was then erased. The digits were chosen from the set 0–9 using a pseudorandom number generator, which formed part of the computer program. A period of 4 seconds then elapsed before the keyboard's bell was rung to indicate that the subject should attempt recall. Rehearsal during the interval was prevented by making the subject read aloud random letters, appearing on the screen at a rate of one per second. This sequence was repeated six times in all.

The entire test was then repeated with a 20-second interval between presentation and recall, again with letters being read out at the rate of one per second to prevent rehearsal.

On each occasion the subject was given one practice run, followed by two control runs, each consisting of six 6-digit numbers. After this the subject was given an intravenous injection, over a period of 60 seconds, of one of the following: methohexitone sodium (1 per cent) 0.15 mg/kg body weight; diazepam (0.5 per cent) 0.05 mg/kg body weight; sodium 4-hydroxybutyrate (20 per cent) 10 mg/kg body weight; sodium chloride injection BP 0.5 ml/kg body weight. Digit recall was tested at 5, 15, 30 and 90 minutes after the injection.

The subject was unaware of the nature of the drug he was receiving. The administrator, though aware of the identity of the drug, was unable to affect the outcome of the test since both presentation and scoring were entirely automatic. The test was then repeated with a different drug on a different day until each subject had received all four drugs. The order was randomized from subject to subject.

The computer subroutine for producing the random numbers and letters was DECUS 5–25 IR,RN Random Number Generator. The oscilloscope display subroutine was DECUS 5/8–23 PDP 5/8 Oscilloscope Symbol Generator (6×4 matrix). Both subroutines are available from the Digital Equipment Corporation Users Society, Maynard, Massachusetts. The main program was original and was written in PDP Assembly Language (PAL III). A listing is available from I.G.G–W.

RESULTS

There was considerable variability between the preinjection performance of the individual subjects (table I).

The increase in the incidence of errors following the injection of the various test drugs compared with the same subject's performance after injection of saline, is given in tables II and III. There was no significant increase in errors with any drug with the 4-second interval. With the test using a 20-second interval, however, there was a significant increase in errors at 5 minutes with all three drugs (methohexitone $P<0.05$, 4–OHB

TABLE II

Increase in errors with 4-second recall interval compared with performance after injection of saline.

	Minutes after injection			
	5	15	30	90
Methohexitone	1.6 ± 1.3	0.3 ± 1.3	−0.3 ± 1.3	1.2 ± 1.6
Diazepam	1.1 ± 2.2	−1.1 ± 2.0	1.3 ± 1.6	1.2 ± 1.3
4-hydroxybutyrate	1.1 ± 1.0	0.9 ± 2.7	−1.4 ± 1.2	1.0 ± 1.3

All results mean ± SEM. No result is statistically significant.

TABLE III

Increase in errors with 20-second recall interval compared with performance after injection of saline.

	Minutes after injection			
	5	15	30	90
Methohexitone	5.9 ± 2.3*	2.4 ± 2.3	−1.6 ± 1.9	2.8 ± 2.0
Diazepam	4.3 ± 1.4**	2.2 ± 1.4	0.3 ± 1.6	2.5 ± 2.7
4-hydroxybutyrate	3.2 ± 1.1*	−0.1 ± 1.5	−3.7 ± 1.8	2.9 ± 2.0

All results mean ± SEM. **$P<0.01$; *$0.01<P<0.05$. The remainder are not statistically significant.

$P<0.05$, and diazepam $P<0.01$). There was no significant increase in the number of errors in the tests at 15, 30 or 90 minutes.

DISCUSSION

Testing of memory by digit retention and the measurement of the effects of drugs upon this is by no means new (Quarton and Talland, 1962; Crow and Bursill, 1970). The method of testing used in this experiment was similar to that used by Crow and Bursill (1970), except that presentation was visual instead of auditory. The present technique has the added advantage that scoring was automatic. Also, by altering certain parameters in the computer program, it was possible to vary independently the number of presentations per test, the digit span, the display time and the interval before recall. The actual values of these parameters used in the experiment were chosen in a series of pilot experiments on different subjects.

During the study it became apparent that the effects of variation in short-term memory from subject to subject could have been taken into account by "titrating" each subject until the test was of sufficient difficulty, e.g., by adjusting the digit span until the pre-drug error rate was at the required level. In any future study this could be achieved by using the existing computer program but varying the appropriate parameter(s). In fact, it is even possible for the computer to adjust such parameters as digit span, display time, etc., automatically in the light of the individual subject's performance. This, and the automatic marking of the test, form the chief justification for using a computer to administer this type of test.

Despite considerable variation in individual performance, statistically significant increases in the error rate were found when the test was administered with a 20-second recall interval, 5 minutes after the injection of each of the centrally active drugs. In each case this test had been preceded by a test with a 4-second interval, in which no impairment of memory was demonstrated.

This failure to demonstrate an effect on recall at 4 seconds is unlikely to be explained by the fact that this test was easier because the error rates in the control situation with intervals of 4 and 20 seconds were comparable (table I). This implies that the increase in errors with the 20-second interval was due to enhancement by the drugs of the decay of the memory trace (Brown, 1958). From this it would follow that, while attention at the time of input is not measurably impaired by the drug effect, the more rapid decay of the memory trace leads to failure of consolidation, and impaired memory.

Recently diazepam in clinical dosage (0.24 mg/kg) has been shown to have a measurable effect upon memory, while having only a minimal effect on decision-making and impairment of intellect (Clarke et al., 1970). This too would support the hypothesis that it is decay of the memory trace which is accelerated by this type of drug, rather than attention which is decreased. Rapid decay of the memory trace would lead in turn to failure of consolidation as suggested by Clarke and associates, and this would result in long-term memory impairment or amnesia.

The dosage of the drugs used in this trial was small, and no dense amnesia or loss of consciousness was expected. One subject did, however, fall asleep 2 minutes after the injection of methohexitone sodium 12.75 mg, but was easily roused by calling her name. Most subjects noted a sensation of light-headedness with all three of the drugs, but in most cases symptoms had disappeared before testing began. In two cases with 4-hydroxybutyrate this sensation persisted until the 15-minute test. One subject complained of lethargy and nausea after the injection of saline; his performance on that occasion was not, however, adversely different.

In the pilot experiments both authors noted a strong subjective sensation of exhaustion towards the end of each series of six 6-digit tests. This felt greater after the injection of one of the drugs under test, and was also commented upon by several of the experimental subjects. The experimental results were analyzed to see if performance deteriorated during the test, by comparing the second half of each series with the first, and by comparing the last third with the first third. This analysis entirely failed to provide any evidence for such an effect of fatigue upon performance. This was so whether or not the series was one in which the total number of errors was increased. We conclude that this sensation of fatigue was adequately compensated by increased concentration on what had by that time become a routine task.

ACKNOWLEDGEMENT

I. G. Grove-White was supported by a Garden Research Fellowship.

REFERENCES

Brown, J. (1958). Some tests of the decay theory of immediate memory. *Quart. J. exp. Psychol.*, **10**, 12.

Brown, S. S., and Dundee, J. W. (1968). Clinical studies of induction agents. XXV: Diazepam. *Brit. J. Anaesth;*. **40**, 108.

Clarke, P. B. (1967). Intermittent anaesthesia for oral surgery; in *Intravenous Anaesthesia—S.A.A.D.*, 3rd ed. (ed. S. L. Drummond Jackson), p. 161. London: Society for the Advancement of Anaesthesia in Dentistry.

Clarke, P. R. F., Eccersley, P. S., Frisby, J. P., and Thornton, J. A. (1970). The amnesic effect of diazepam (Valium). *Brit. J. Anaesth.*, **42**, 690.

Crow, T. J., and Bursill, A. E. (1970). An investigation into the effects of metamphetamine on short term memory in man; in *Amphetamines and Related Compounds* (eds. E. Costa and S. Garathini), p. 889. New York: Raven.

Frumin, M. J., Herekar, W., and Jarvik, M. E. (1969). The amnesic effects of diazepam and scopolamine in man. *4th Intern. Congr. Pharmacol.*, Basle, p. 289.

Jorgensen, N. B., and Leffingwell, F. E. (1953). Premedication in dentistry. *J. S. Calif. dent. Ass.*, **21**, 25.

O'Neill, R., and Verril, P. J. (1969). Intravenous diazepam in minor oral surgery. *Brit. J. oral Surg.*, **7**, 12.

Quarton, G. C., and Talland, G. A. (1962). The effects of methamphetamine and pentobarbital on two measures of attention. *Psychopharmacologia*, **3**, 66.

BOOK REVIEW

The Principles and Practice of Clinical Trials. Based on a Symposium organized by the Association of Medical Advisers in the Pharmaceutical Industry. Edited by E. L. Harris and J. D. Fitzgerald. Published by E. & S. Livingstone, Edinburgh and London. Pp. 254; indexed; illus. Price £3.00 net (U.K. price).

In the past, communications between the pharmaceutical industry and the practising clinician have been far from satisfactory. It is probably true that the fault lay more with the clinicians than with the industry and certainly the fact that the situation is very much improved today is largely due to those medical advisers who have made a positive effort to develop communications. This short monograph of approximately 250 pages on the *Principles and Practice of Clinical Trials* is an excellent example of the efforts that have led to better relations between the two groups.

The monograph is based on a symposium organized by the Association of Medical Advisers in the Pharmaceutical Industry and held in the Royal College of Physicians in London in February 1969. In addition to a terse and pertinent foreword by Sir Max (now Lord) Rosenheim the text contains some twenty-eight papers presented in two sections and includes contributions from industrial laboratories, from departments of basic sciences and clinical pharmacology, and from a range of other clinical departments such as cardiology, medicine and psychiatry.

The first section deals with virtually every aspect of the clinical trial from the development of a drug to the method of preparing and publishing the subsequent reports. The advice is sound and there will be few clinicians who will not benefit from a careful study of the individual papers; those on statistical methods are particularly recommended even to readers who claim a broad familiarity with the subject.

The second and smaller section devoted to practical applications is less satisfactory, not because the individual contributions have failed to maintain the earlier standard, but because the cover is less comprehensive. There is surely a lack of balance in a section containing eleven papers, four of which are concerned with psychotropic drugs and not one is devoted to the problems involved in the evaluation of analgesic drugs. Admittedly the initial responsibility for this lies with the symposium organizers and not with the editors who deserve to be congratulated on producing a volume which is both readable and informative. Nevertheless the exercise of a little editorial licence in including one or two papers on those aspects not covered by the symposium would have added immensely to the value of this book.

This, however, is the only major criticism. At a minor level the occasional use of American versions of spelling is irksome in a British book and again a few typographical errors have crept in; one that needs correction is the expression of blood cholesterol in children in ml instead of mg on page 173.

On the production side the text is printed on good quality paper firmly bound; the print is easy to read and the figures are mostly simple and unambiguous. Almost certainly this book will become compulsory reading for all doctors interested in clinical trials.

J. P. Payne