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THE DIFFERENTIAL EFFECTS OF MECLOFENOXATE ON MEMORY LOSS IN THE ELDERLY

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Summary

A double-blind study of the effects of meclofenoxate on memory performance of fit, able, elderly subjects was carried out. A number of performance measures, designed to measure various aspects of memory function were employed. These revealed that meclofenoxate appears to increase the consolidation of new information into long-term memory, but does not affect other aspects of remembering.

It was also found that significantly more of the subjects receiving meclofenoxate reported an increased level of mental alertness.

INTRODUCTION

It is widely recognized that a degree of mental impairment is one of the major problems associated with old age. As well as the personal suffering involved, brain failure in the elderly produces a large drain on health services, which will increase over the next 25 years as the size of the elderly population continues to grow. Faced with this problem, it is not surprising that various drugs have been investigated in an attempt to discover a 'cerebral activator'. One such compound which has been widely studied is meclofenoxate (Lucidril).

Meclofenoxate was first synthesized at the French National Research Centre, by combining dimethylaminoethanol with *p*-chlorophenoxyacetic acid, a synthetic substance chemically related to the plant growth hormone, auxin. The hydrochloride of the resulting compound, 2-dimethylaminoethyl 4-chlorophenoxyacetate hydrochloride, a white solid soluble in water, was given the approved name meclofenoxate by the World Health Organisation. While its action has still to be described fully, meclofenoxate has been shown to reduce markedly the accumulation of lipofuscin granules in aged guinea-pigs (Nandy & Bourne 1966). Histochemical studies with guinea-pig brains (Nandy 1968) have demonstrated that meclofenoxate reduces the activity of succinic and lactic dehydrogenases and enhances the activity of glucose-6-phosphate dehydrogenase, suggesting that its effect is to enhance cellular metabolism by activating the 'pentose shunt' pathway. The demonstration of meclofenoxate's ability to enhance the resistance of cerebral cells of rats, mice and rabbits to various forms of oxygen deprivation, including cyanide intoxication (Nakajima & Thuillier 1964, Rump & Edelwejn 1968), reduced atmospheric pressure (Nickel et al. 1963) and reduced oxygen tension (Dereymaeker et al. 1962) in the inspired air, provides confirmation of the suggestion that meclofenoxate operates through the enhancement of alternative pathways of glucose metabolism.

Over the past decade, meclofenoxate has been the subject of a large number of clinical trials designed specifically to measure its effectiveness in combating mental impairment in a variety of clinical groups of elderly human subjects. Unfortunately, many of the early studies reported in the literature are of little or no value, due to weakness in design or the statistical treatment of the results. In particular, failure to control for placebo effects by the use of a double-blind procedure is common. However, even when the discussion is confined to studies which cannot be faulted in this way, the results are still equivocal. For example, Gedye, Exton-Smith & Wedgwood (1972) using a double-blind, matched pairs, partial cross-over design, compared the learning performance of two groups of elderly, mildly demented patients. They reported that:

'The treated groups all improved with respect to their controls, a result which is encouraging and warranting further work on . . . the effects of meclofenoxate.'

This finding contrasts sharply with the results of an earlier trial reported by Oliver & Restell (1967). They employed a double-blind, cross-over design to assess the reaction to meclofenoxate of geriatric patients exhibiting a variety of symptoms associated with intellectual deterioration. Performance was examined by a battery of eight tests designed to measure mental function. In no case was there a significant effect due to meclofenoxate; a finding which led Oliver and Restell to conclude:

'There is no indication that meclofenoxate therapy influenced any particular group of patients, or test results, in this trial.'

In order to reconcile these apparently contradictory findings, it is necessary to consider in some detail what is known of the behavioural characteristics of the memory system. There is now a large body of evidence which shows that even the most commonplace acts of remembering are not underlaid by a static, unitary system. Rather, they are the products of a multi-process system in which the original input is continually being transformed and reorganized. For example, the recall of verbal information can be viewed as being the product of a three-stage system. The three stages are sensory, primary and secondary memory, each of which has its own operating characteristics. Sensory memory is input-modality dependent with a rapid decay rate, information being lost within a few seconds at the most. Primary memory is largely independent of input modality, coding being on an acoustic/articulatory basis. It has a limited capacity, and is easily disrupted by concurrent activity. Secondary memory is also independent of input modality, but employs semantic coding and is resistant to decay during concurrent activity. Failure to recall from secondary memory is due at least in part to an inability to retrieve information which is still potentially available. (For a more detailed discussion see Marcer 1974.)

The implications of the preceding analysis for drug trials of the sort under consideration here are obvious. If remembering is the product of more than one 'store' then it follows that a breakdown of any one of them is, under certain circumstances, likely to produce forgetting. However, this would only be made apparent by employing a test appropriate to the particular 'store' under investigation. For example, the digit-span test is a good measure of primary memory functioning, but is quite inappropriate for measuring, say, efficiency of secondary memory retrieval processes. It follows, therefore, that any trial of the effectiveness of a drug in improving memory must first specify which

aspect of memory is being investigated, and then apply the appropriate test. It is no more reasonable to assume that a drug will improve all aspects of memory equally, than it is to assume that all aspects will have deteriorated with age to the same extent. Viewed in this light, the apparently contradictory results of the two trials discussed earlier become less puzzling. The performance measure employed by Gedye et al. (1972) was a complex, paired associate learning task, in which speed of processing was an important factor. Such a test would have a large secondary memory component. In particular, efficiency of performance would depend heavily upon the rate at which new information could be transferred from primary to secondary memory. The Oliver & Restell (1967) study on the other hand emphasized tests which rely on primary memory for their performance. These included digit-span, counting backwards, and continuous subtraction in steps of three. Moreover those tests which did have a secondary memory component probably emphasized the ability to retrieve old information, rather than store new material.

The trial reported here investigated the hypothesis that the beneficial effect of meclofenoxate in old age is specific to certain stages in the memory system.

Subjects

Seventy-six patients (44 men and 32 women) drawn from three local practices completed the psychological component of the trial. These patients were selected as suitable from an original pool of 250, of whom 70 declined to enter the trial. The remainder were given a detailed medical examination by a senior registrar from the Geriatric Unit at Southampton, and were screened for intellectual deterioration by one of the psychologists. Eighty-four patients were rejected as being unfit to enter the trial. A further 10 indicated that they no longer wished to participate because they had not originally realized the extent of the commitment involved.

Of the 86 subjects remaining, 10 (6 on meclofenoxate and 4 on placebo) discontinued their tablets and 14 had a change of mind about taking the tablets. The reason they gave for this was that their health was already good, and they 'didn't need to take anything'. However, as these subjects were all willing to undergo the various assessments, they were kept in the trial as an untreated control group. In order to obtain baselines, a group of 18 student nurses, mean age 19.5 years, was asked to perform the memory tests.

Method

The trial was double-blind, subjects being allocated at random to the two treatment conditions. The active group took meclofenoxate 600 mg twice daily while the placebo group was identically treated with an inert compound. Each subject was studied for a total of 9 months but in case there were any withdrawal symptoms, medication ceased after 6 months. Tablets were delivered to the subject's home at 3–4 weekly intervals by the senior registrar. Urine samples were taken at random intervals and analysed for the presence of meclofenoxate. These showed that failure to take tablets was not a problem in this study. There were four psychological assessments, at 0, 3, 6 and 9 months. In order to control for time-of-year effects, the rate of entry into the trial was such that as the last batch of subjects was entering, the first batch was undergoing the 6-months assessment.

Procedure

(a) *General interview*

At the first task session a considerable period was spent talking about the patient's life history, including such areas as interests, past occupation, family background etc. With the patient's permission this interview was tape-recorded, thus enabling the tester to interact more freely with the patient.

(b) *Memory tests**

As its measurement requires elaborate electronic equipment, no tests of sensory memory were used in this trial. In all, five tests were employed.

(i) *Free recall.* Subjects listened to a list of 10 words which were then recalled in any order. The process was repeated until a criterion of 70% recall was attained. By measuring how many words are learned over a series of trials, this test provides a measure of learning ability, while subsequent recall scores provide a good index of retention based upon secondary memory.

(ii) *Digit-span.* Subjects recalled in correct order strings of digits of increasing length. This test is a good index of primary memory.

(iii) *Recognition test.* Subjects were shown a series of photographs of prominent people and asked to name them. If unable to do so, subjects were provided with cues in the form of three names, the correct one plus two others of personalities of similar background from the same period. This test measures two aspects of secondary memory. The uncued condition shows to what extent the subject is able to gain access to the appropriate set of responses and select the correct one. The cued condition performs the first half of this process for the subject. Failure in the cued condition, therefore, reflects an inability to match the correct response with the stimulus input.

(iv) *Past events test.* This test is similar to the recognition test in that it measures the ability to enter secondary memory and retrieve very old information. It required the subject to answer questions about past events, the answers to which it is reasonable to assume he would at one time have known.

(v) *Prose passage test.* This test required the subject to answer questions about a short prose passage. It provides a measure of memory for meaningful material as well as comprehension.

(c) *Post-trial questionnaire*

At the end of the trial each subject was asked to complete a questionnaire. As well as being asked for opinions about the organization of the trial, subjects were asked two questions about their health. These were:

(i) How do you rate your health now, compared with when the trial began?
(ii) What effect, if any, did the tablets have?

Results

Of the 76 patients entering the trial, two, both receiving placebo, dropped out through illness, and one control patient died. Thirty-one patients receiving meclofenoxate, 29 patients receiving placebo and 13 untreated control patients completed the trial. The average age of each group was, active 72.19 years, placebo 73.24 years and control 70.07 years.

Statistical Analysis

In all cases except the post-trial questionnaire, performance of the two treatment groups was compared using a split-plot analysis of variance with one repeated factor (sessions) and one non-repeated factor (active versus placebo). The data from the untreated control group and the young nurses were not included in the statistical analysis, but are reported as interesting comparisons. Apart from the delayed free-recall test, the untreated controls consistently outperformed the two treatment groups. This finding confirms the control patients' own evaluation of their well-being.

(i) a *Immediate free-recall*

A score for each subject was calculated by counting the number of words recalled on the first two trials. These scores are shown in Table I. There was no significant difference

* Fuller details of the test materials are available from the first author.

Table I. Mean immediate free-recall scores for the first two trials

Group	*Months*			
	0	*3*	*6*	*9*
Drug	8.93	9.28	9.74	9.21
Placebo	9.50	9.62	10.20	9.70
Control	11.09	11.50	11.10	11.89
Nurses	14.90	—	—	—

between active and placebo on this test, the slight pre-treatment superiority of the placebo group being maintained throughout the trial.

(i) b *Delayed free-recall*

Each individual's delayed recall score was expressed as a percentage of his score on the final learning trial. These scores are shown in Table II. The superiority of the active

Table II. Mean percentage delayed recall

Group	*Months*			
	0	*3*	*6*	*9*
Drug	63.4	79.4	66.1	65.3
Placebo	63.4	51.8	55.8	57.2
Control	61.6	64.4	76.9	67.1
Nurses	75.9	—	—	—

group is highly significant ($P < 0.01$) as is the treatment × session interaction ($P < 0.01$). The interaction is due to the difference between the two groups not emerging until the second session.

(ii) *Digit-span*

The mean digit-span scores for each group are shown in Table III. There was no significant difference between the two treatment groups nor was the interaction significant.

Table III. Mean digit spans

Group	*Months*			
	0	*3*	*6*	*9*
Drug	5.65	5.69	5.43	5.88
Placebo	6.00	6.04	5.96	6.09
Control	5.75	6.36	6.36	6.70
Nurses	7.07	—	—	—

(iii) *Recognition*

The mean numbers of faces identified under the cued and uncued conditions are shown in Table IV. There was no significant difference between the two treatment groups,

Table IV. Mean recognition scores under cued and non-cued conditions

Group	3 Months		6 Months		9 Months	
	Cued	*Non-cued*	*Cued*	*Non-cued*	*Cued*	*Non-cued*
Drug	9.43	6.67	9.52	6.95	9.70	7.25
Placebo	9.55	6.65	9.85	6.95	10.35	8.41
Control	11.00	8.63	10.70	9.00	11.40	10.20
Nurses	6.00	5.30	—	—	—	—

nor was the interaction significant. The fact that the elderly scored higher than the nurses on this test offers some support to the belief that this test was tapping long-term memory processes. It is also interesting to note that cues increased recognition considerably in the case of the elderly ($P < 0.01$) but not the young. This is in accord with the view that part of the elderly subject's memory difficulty lies in the retrieval of information which is in storage, but inaccessible at the time of recall.

(iv) *Past events*

Individuals were scored one point for a correct answer, giving a maximum possible score of 16. These scores are shown in Table V. There was no significant difference

Table V. Mean recall of remote events

Group	Months		
	3	*6*	*9*
Drug	9.76	9.29	8.78
Placebo	9.32	9.33	8.71
Control	11.18	10.33	12.00
Nurses	5.64	—	—

between the two treatment groups, nor was the interaction significant. As with the recognition test, the nurses performed less well than any of the elderly groups.

(v) *Prose passage*

Mean scores out of a maximum of 20 are shown in Table VI. There was no significant difference between the two treatment groups, nor was the interaction significant.

(vi) *Post-trial questionnaire*

The subjective ratings of (1) health change and (2) effect of tablets were analysed using a χ^2 test. There was no significant difference between the two treatment groups for

Table VI. Mean scores on prose passage

Group	*Months*			
	0	*3*	*6*	*9*
Drug	6.80	6.47	7.13	9.12
Placebo	7.35	8.59	8.13	7.87
Controls	10.00	11.63	10.63	12.43
Nurses	12.50	—	—	—

the health assessment. However, 67% of the active group reported that the tablets had had a beneficial effect compared with 42% of the placebo group. This difference is significant ($P < 0.05$).

Discussion

This study differed from earlier trials of meclofenoxate in that the subjects were all in good health. This is borne out by the fact that nearly all were living actively in the community and scored high on the MSQ test. Moreover, the fact that only one patient died, along with the low drop-out rate is further evidence of these subjects' well-being. Nonetheless, as a comparison with the nursing students' data makes clear, they were suffering from a measurable amount of intellectual deterioration.

Despite the difference in the physical and mental well-being of the subjects, the results of this trial are consistent with those of the two studies discussed earlier. For example, the failure of meclofenoxate to improve primary memory function, as measured by digit-span, confirms the finding of Oliver & Restell (1967). Similarly, the failure to find differences on the past events, recognition, and prose tests indicates that there was no improvement in secondary memory function which required the retrieval, recognition or matching of material already assumed to be in store. However, there is evidence from the free-recall test to suggest that meclofenoxate does improve the ability to transfer new information into secondary memory.

Unlike the prose test, the free-recall test was not composed of material that could be readily related to experience in the subject's own life history. However, the fact that there were no constraints on the *order* of recall of the words means that a degree of recoding at input was possible. There is ample evidence to show that free-recall performance can be significantly increased by reorganizing the stimulus material at input to take account of associative relationships existing between non-adjacent list items (Matthews, Marcer & Morgan 1964). In terms of the conceptual model used here, the effect of this reorganization is to shift information from primary to secondary memory. Once the information has been encoded into secondary memory it will not be displaced or undergo decay while new material is being attended to. Thus to perform well in the delayed free-recall test, a subject would need to have placed the stimulus material into secondary memory. In the immediate free-recall test, however, enough information would still be present in primary memory to produce efficient recall. Viewed in these terms, the superior delayed free-recall of the meclofenoxate group, without a corresponding effect in immediate free-recall, suggests that this group was more efficient at organizing new input into long-term memory. While the variables affecting input organization are complex, it is

clear that the rate at which the subject can process new information is crucial. Thus the finding that this is the only test where the active group *consistently* out-performed the placebo group is consonant with the view that the effect of meclofenoxate is to allow the elderly to process complex new information more quickly. This theoretical interpretation of the data is, of course, speculative, and the atypical performance of the placebo and control groups suggests that some caution is required in discussing these data. However, it is in line with the findings reported by Gedye et al. (1972), who also used a performance measure that involved the coding of complex new information and used total decision time to estimate performance.

The post-trial questionnaire data imply that the increase in memory function measured by the free-recall test was, in a number of cases, accompanied by an improvement in the carrying out of day-to-day activities. While the meclofenoxate group reported no significant gain over the placebo group in their health, significantly more of them did report that the tablets had done them some good. Further investigation showed that subjects equated the term 'improvement in health' with specific conditions such as bronchitis, arthritis and other complaints associated with old age. Clearly meclofenoxate had no effect upon this aspect of health. On the other hand those subjects who reported a beneficial effect of meclofenoxate consistently used terms like 'increased alertness' and 'feeling of well-being' to describe the change.

It is recognized that the tests employed in this trial are of an academic nature. However, the finding that meclofenoxate appeared to assist the process of consolidating information into secondary memory is an important one, as it is commonly accepted that it is this aspect of memory functioning which is most adversely affected by normal ageing.

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