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The Effect of Cyclandelate on Mental Function in Patients with Arteriosclerotic Brain Disease

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The manifestations of the chronic brain syndrome associated with cerebral arteriosclerosis are notoriously diverse, ranging from disturbance of cerebral functions which can be recognized by physical examination to those which can be identified by examination of the patient's mental state. With widespread arteriosclerotic involvement of the cerebral circulation there are important alterations in the individual's thinking and behaviour. There is disturbance of memory, accompanied by disorientation, at first in time and place and later as to person; and intellectual functions including comprehension, problem solving, learning, and judgement are also impaired.

Admissions of patients to psychiatric hospitals with diagnoses of 'chronic confusional state', 'arteriosclerotic dementia', or 'chronic brain syndrome with arteriosclerosis' are increasing and constitute a major mental health problem. Generally, those patients with arteriosclerotic brain disease referred to psychiatric hospitals have gross impairment of psychological functions with little or no clear evidence of motor or sensory defects. These disturbances in thought and behaviour may be attributed largely to cerebral anoxia produced by arteriosclerosis, although one must remember that the eventual clinical picture can be influenced by social and environmental conditions and psychological factors.

Treatment regimes for this group of patients are essentially restricted to maintenance of nutrition, limited occupational activities and control of disturbed behaviour with phenothiazines and/or sedation.

Attempts to enhance cerebral circulation have been restricted by the resistance of cerebral blood flow to modification and the fact that blood flow to the brain seems less readily influenced by drugs than those in any other tissue. Recently, however, there have been a number of reports in the medical literature that cyclandelate (Cyclospasmol) produces dilatation of cerebral vessels (Eichorn, 1965; Kuhn, 1966) and increases the cortex perfusion rate (O'Brien and Veall, 1966); and an improvement in mental function in elderly patients treated with cyclandelate was reported by Drift in 1961; Ravina, 1963; Ward, 1964; and by Ball and Taylor in 1967. In view of these encouraging reports it was decided to assess the effect of cyclandelate on the mental functioning of patients admitted to a psychiatric hospital with circulatory brain disease.

Selection of Patients

The problem of distinguishing clinically cerebral arteriosclerosis from senile dementia, Alzheimer's Disease, and Pick's Disease has always presented considerable difficulty. The onset of symptoms pointing to a brain disorder produced by circulatory disease usually occurs between 65 and 75 years of age, although it is well recognized that the disease may appear at a much younger age, and one of the main difficulties in differential diagnosis is that cerebral vascular disease and senile changes in the brain can occur *simultaneously*. It has been found that both types of pathology are seen in more than 20 per cent of patients with chronic brain diseases examined post mortem, and as both diseases can occur in the same individual it is sometimes impossible to distinguish the diseases during the patient's lifetime (Busse).

The patients selected for this trial were all in-patients at Whitchurch Hospital, Cardiff, in whom the history and examination indicated a diagnosis of cerebral arteriosclerosis. They all

complained at some stage in their illness of faintness, dizziness and headache, with gradual increase in memory impairment, eventually progressing to marked confusion and disorientation. In over half the patients the onset of their illness was reported as sudden, and in 75 per cent there was evidence of actual fainting attacks or convulsions.

Their outstanding disability was severe impairment of mental functions, and there was little or no detectable neurological disability.

Clinical examination and investigation excluded other causes of chronic confusional states, such as deficiency disease, epilepsy, intracranial tumour, and syphilis. There were 40 patients, 15 male and 25 female, ranging in age from 62 to 75 years.

Method

The trial was conducted using the double-blind crossover technique with placebos, and consisted of two × two months treatment periods separated by a two-week period of no-treatment. During the trial the patients received no medication other than the trial materials and a mild, non-barbiturate hypnotic when considered necessary.

Parameters

Mental function in the trial was assessed using the following tests:

1. *The Bender-Gestalt test*

This was chosen because it normally indicates changes in perceptual functioning and motor control. The patients were asked to draw a group of designs which were set in front of them, one card at a time. Each patient was assessed at the beginning of the trial to obtain a base-line and thereafter at fortnightly intervals. The time taken to complete the test was also recorded.

2. *The Digit-span test*

Directly following the Bender-Gestalt test, the digit-span test was applied to each patient and the results recorded as:

(a) Digits forwards.
(b) Digits backwards.
(c) Total digits forwards and backwards.

3. *The Parkside Behaviour Rating Scale* (*See Annexe*)

This rating scale was employed to assess changes in the patient's behaviour within his environment. This was assessed for each patient by the senior nursing staff at the beginning of the trial, and thereafter at fortnightly intervals. The assessment of any one patient's condition was carried out by the same individual on each occasion.

Each patient was assigned a trial number, and for the purposes of the fortnightly assessments the patients were divided into four groups, A, B, C, and D, and the group to which any patient was assigned was recorded on the entry form. The four groups commenced treatment at intervals of twenty-four hours.

It was necessary to assign to each patient a group order number (from 1 to 10) so that patients could be assessed in exactly the same order on each occasion.

In recording the Parkside Behaviour Rating Scale, the nursing staff were asked to place a tick opposite each parameter in the appropriate column. The records of each assessment were then filed, and at no time during the trial were the results of any previous assessment consulted.

Tablets were supplied in identical bottles, each bottle containing two-months supply. Each bottle was marked with a number representing the patient's trial number and a letter A representing the first two-months treatment, or a letter B representing the second two-months treatment. The treatments were fully randomized and the code held by Brocades (Great Britain) Limited. Each patient received one tablet four times daily, the material being Cyclospasmol tablets 200 mg. and identical placebos. The drug was extremely well tolerated and no side-effects were observed by the nursing staff which necessitated interruption of administration.

Results

The data collected during the investigation were analysed by carrying out a series of analyses of variance. Such an analysis of variance has been carried out on each of the Parkside scales, the Bender-Gestalt scores and time taken on

this test, and on the digit-span test. The analyses of variance were tested for significant differences between drug and placebo treatments averaged over the entire period of the trial, for initial and persistent differences between the two groups of patients irrespective of treatment, and for differences in trend in the performances of drug and placebo-treated patients over the individual occasions of assessment and for the first and second two-month periods of the trial. It is in these differences in trend that any distinct effect of the drug on the performances of patients would be revealed.

The findings to emerge from these analyses of variance in the data are shown in Table I.

Although a change in the direction of clinical improvement was found in all but two variables over time regardless of medication, four are significantly affected by the drug over and above this general tendency.

Orientation, and Communication + Socialization, are both significantly affected by administration of the drug. Although both these variables are affected adversely at the beginning of each treatment session (of the drug), this is rapidly overcome, and after two weeks the 'drug' patients are scoring higher in these variables than are the 'placebo' patients. In fact, the difference in linear trend between the 'drug' and 'placebo' patients over time is highly significant ($p < \cdot 001$) for both variables.

The difference in linear trend is not significant for mood-environment interaction or self-care, but there is an overall difference in these variables between placebo and drug ratings. As in Orientation and Communication + Socialization variables, the 'drug' patients are initially rated worse than the controls, but within a fortnight the former have increased their scores to well above those of the latter.

Digit-span is also significantly ($p < \cdot 05$) affected by the use of the drug, the 'experimental' patients having a higher digit span score than the controls, although this difference did not differ significantly over time (i.e. within any one month).

There is no significant difference between drug-treated and control scores on the 'psychotic rating scale' and the 'Bender test', the 'time' measure, or for the Co-operation and Occupation ratings.

Discussion

Cyclandelate is now generally accepted as

Table I

Summary of analyses of variance findings

	Drug *v.* placebo	Ratings over 2 mths.	Linear trend in ratings	Groups I *v.* II	Occasions 1st 2 mths. *v.* 2nd 2 mths.	Drug × rating interaction	Linear trend drug *v.* placebo
Parkside scale							
Self care	N.S.	$< \cdot 05$	$< \cdot 05$	$< \cdot 05$	N.S.	$< \cdot 01$	N.S.
Orientation	$< \cdot 001$	$< \cdot 001$	$< \cdot 001$	N.S.	N.S.	$< \cdot 001$	$< \cdot 001$
Communication + socialization	N.S.	$< \cdot 05$	$< \cdot 01$	N.S.	N.S.	$< \cdot 05$	$< \cdot 001$
Psychotic behaviour	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Co-operation + occupation	N.S.	$< \cdot 05$	$< \cdot 01$	N.S.	$< \cdot 01$	N.S.	N.S.
Mood + environment interaction	N.S.	$< \cdot 05$	$< \cdot 001$	N.S.	$< \cdot 05$	$< \cdot 01$	N.S.
Bender	N.S.	$< \cdot 01$	N.S.	N.S.	N.S.	N.S.	N.S.
Time	N.S.	N.S.	N.S.	$< \cdot 001$	N.S.	N.S.	N.S.
Digit span	$< \cdot 05$	$< \cdot 05$	N.S.	N.S.	N.S.	N.S.	N.S.

N.S. = Not significant.

$\cdot 05$, $\cdot 01$, $\cdot 001$ = Probability that difference is greater than chance.

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an effective treatment for many peripheral vascular diseases by virtue of its direct action as a vasodilator. There would also appear to be reliable evidence that the drug improves the cerebral circulation.

Gentili *et al.* (1962), using rheoencephalography, and Kuhn (1966), using retrograde brachial cerebral angiography, have shown that cyclandelate reduces arterial vasospasm and improves cerebral blood flow; and Eichorn (1965), employing cerebral radioserialography, has demonstrated an increase in blood volume and a reduction of the pathologically-lengthened circulation time in cases of cerebro-vascular insufficiency. It is suggested that cyclandelate acts predominantly in the arteriolar and capillary areas, increasing cerebral perfusion and leading to a re-distribution of blood with increase in areas where it is required, especially ischaemic areas.

Complementary to this objective evidence of the action of cyclandelate in increasing cerebral cortex-perfusion rate, there have been a number of reports suggesting clinical improvement in elderly, arteriosclerotic patients, following the use of the drug. (Ward (1964); Ball and Taylor (1967).)

This assessment of cyclandelate was made on 40 patients who had required admission to a psychiatric hospital and who were representative of a group of patients which is making ever-increasing demands on psychiatric and geriatric services. There was serious impairment of all mental functions and little possibility of their ever being discharged from hospital.

The results indicate that cyclandelate does produce improvement in certain parameters, especially those of Orientation, Communication, and Socialization, as compared to placebo. There was also an overall difference between placebo and drug ratings for the variables Mood-Environment Interaction and Self-Care, which, however, showed no significant difference in linear trend. It is interesting that both initial variables are affected adversely at the commencement of treatment, but after two weeks an improvement is evident, suggesting in clinical practice the importance of continuing with the drug for some weeks before expecting any improvement in behaviour.

It is suggested, in view of these findings, that cyclandelate may be regarded as a useful addition to present treatment regimes for patients suffering from arteriosclerotic brain disease.

Summary

A double-blind crossover trial is described in which the effect of cyclandelate is assessed on 40 patients admitted to a psychiatric hospital who were severely handicapped with symptoms due to arteriosclerotic brain disease. Significant improvement was observed in a number of important mental functions, suggesting that enhancing the cerebral circulation produces a favourable clinical response in this category of patient.

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Annexe

The Parkside Behaviour Rating Scale (PBRS)

The following is a short explanation of the Parkside Behaviour Rating Scale. Copies of the Scale and its associated record sheet are available, on request, from Brocades & Co., Ltd., Trend House, Pyrford Road, West Byfleet, Surrey.

The Scale is based upon the assessment of the patient's behaviour within his environment. The parameters are listed under six main headings.

Self-care.

Orientation.

Communication and Socialization.

Psychotic Behaviour.

Co-operation and Occupation.

Mood and Reaction to Environment.

Several sub-headings are included under most of the above. Against each sub-heading is indicated in vertical columns numbered 1 to 5, a description of that parameter graded in severity from 1 (severest) to 5 (least severe). For example, under the main heading of Self-care, sub-heading a, appear the following descriptions, aligned horizontally.

1. Requiring every form of nursing care.
2. Requiring regular nursing supervision.
3. Usually attends to own personal habits.
4. Verbal. Verbal nursing care only.
5. Border.

The assessor indicates by a tick in the appropriate column the description most nearly appropriate to the patient under assessment. A numerical score may therefore be obtained.

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