CYCLANDELATE AND MENTAL FUNCTIONS:
A DOUBLE-BLIND CROSS-OVER TRIAL IN NORMAL ELDERLY SUBJECTS

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Summary
The action of cyclandelate was assessed using simple mental function tests in 114 normal elderly patients. The trial was completed by 54 patients and a statistically significant improvement in intelligence was found in the females. The implications of this result are discussed.

Introduction
Cyclandelate (Cyclospasmol*) is the mandelic acid ester of 3,3,5-trimethylcyclohexanol. The pharmacological studies of Bijlsma, Funcke & Tersteeg (1956) show that cyclandelate is an active ester with about three times the potency of papaverine but with less toxicity. Its action is exerted on smooth muscle with no significant effect on blood pressure or heart rate. Numerous workers (Gillhespy, 1959; Hornstein, 1961; Sherber, 1963; Spencer, 1963; Fremont, 1964; and Ross, 1965) have shown the clinical value of cyclandelate in peripheral vascular disorders, and in cerebrovascular disease subjective evidence of the value of cyclandelate has been demonstrated by van der Drift (1961), Ravine (1963), and Ward (1964). Eichhorn (1965), using cerebral radiocirculography, Luisada & Jacobs (1969), using rheoencephalography, and O'Brien & Veall (1966), using xenon wash-out, have objectively measured improvement in cerebral blood flow following use of the drug. Improvement in mental functions with cyclandelate has been demonstrated by Ball & Taylor (1967), Smith & Lowrey (1968) and Fine et al. (1970). All previous studies on cerebral function have been carried out on patients with severe intellectual impairment from varying causes. It was thought worthwhile to set up a study on normal elderly people living at home who in everyday conversation appeared to be mentally normal, but in whom psychometric testing revealed minimal intellectual impairment.

Method
The trial was carried out on healthy volunteers in group practice near Glasgow.

Subjects
The nature of the trial was explained to 114 subjects over the age of 65 (45 men and 69 women). Of these 14 were discarded, one of each sex who were too well mentally, three men and five women who were too ill physically, and two men and two women who were too psychiatrically ill for inclusion. Four women and one man declined to enter the trial, there were two deaths, and

* Cyclospasmol—Brocades (G.B.) Ltd.
there were 39 defaulters (23 women and 16 men). The number of patients actually entering the trial was 54 (31 women and 23 men).

**Testing procedures**

All patients were assessed, both before and during the trial, on a battery of psychiatric and psychological assessment and testing procedures. These assessments were carried out by an independent observer. The actual tests employed have been described previously in some detail by Judge (1971); essentially the battery consisted of the following:

1. A psychiatric questionnaire based on the Tavistock questionnaire, consisting of 16 items relating to specific psychiatric symptoms. (Maximum score = 16; low scores represent freedom from psychiatric illness.)
2. The Mill Hill Vocabulary Scale (maximum score = 17).
3. Raven's Coloured Progressive Matrices (maximum score = 36).
4. A simple memory task, based on five minutes' delayed recall of a name and address together with the name of a flower and a colour (maximum score = 10; high scores represent unimpaired learning).
5. A brief intelligence test, developed for use with geriatric patients at the Crichton Royal Hospital by Robinson (maximum score = 24; high scores represent unimpaired intelligence).
6. An Attitude Questionnaire, developed in the Psychology Department of Glasgow University by Weir, which assesses consistency and shifts in attitudes.
7. A simple Paired-Associate Learning Task consisting of five pairs, in which three are of high association level and two of low association level of difficulty (maximum score = 5; high scores represent good learning capacity).

**Trial procedure**

A strict double-blind cross-over technique was used. Patients were assessed on the battery of tests of mental functions prior to commencement of the trial, and were then allocated at random to active or placebo treatment during the first phase of the trial. This initial phase of treatment lasted for one month at the end of which mental function tests were repeated. There now followed a one-month period in which no treatment was administered, at the end of which patients were crossed-over for the one-month treatment of the second phase of the trial. Final assessment of mental functions took place at the end of this second treatment period. Whilst on active treatment within the trial each patient received 1200 mg Cyclospasmol daily.

**Results**

The findings derived from the testing procedures employed in this trial have been analysed by means of an analysis of variance. Within this analysis comparisons of trends were examined for active and placebo treatments in relation to the pre-trial level of each patient. The analysis also examined the differences between males and females in terms of responsiveness to the active and placebo treatments, and the effects of order of administration of these treatments within the cross-over design (active first/placebo second versus placebo first/active second).

Table 1 shows the average increase or decline of raw scores from the pre-trial levels of each patient on each of the tests. These deviations from the pre-trial levels are shown for female and male subjects whilst receiving active and placebo treatments.

The data derived from the Attitudes Scale were found to be too complex for analysis, due to the compound nature of the scores, and these have been excluded from further discussion.
Table I: Mean changes in performance during active (Cyclospasmol) and placebo treatments from pre-trial levels

<table>
<thead>
<tr>
<th></th>
<th>Active Females (N = 31)</th>
<th>Active Males (N = 23)</th>
<th>Placebo Females (N = 31)</th>
<th>Placebo Males (N = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric Questionnaire</td>
<td>0.19</td>
<td>0.56</td>
<td>0.19</td>
<td>0.34</td>
</tr>
<tr>
<td>Mill Hill Vocabulary Scale</td>
<td>0.39</td>
<td>0.09</td>
<td>-0.06</td>
<td>-0.04</td>
</tr>
<tr>
<td>Raven's Coloured Matrices</td>
<td>0.52</td>
<td>0.17</td>
<td>-0.77</td>
<td>-0.26</td>
</tr>
<tr>
<td>Memory</td>
<td>0.85</td>
<td>-0.13</td>
<td>0.87</td>
<td>0.04</td>
</tr>
<tr>
<td>Intelligence</td>
<td>0.80</td>
<td>-0.26</td>
<td>0.10</td>
<td>0.17</td>
</tr>
<tr>
<td>Paired-Associate Learning</td>
<td>0.52</td>
<td>-0.30</td>
<td>0.03</td>
<td>0.13</td>
</tr>
</tbody>
</table>

The statistical analysis of the findings shown in Table I reveals a number of significant findings and points of interest. Firstly it was found that for the trial as a whole the data collected from the male patients lacked homogeneity of variance, and it appeared that an undisclosed variable was operating to distort the findings from these patients. It is perhaps worth noting that on the psychiatric questionnaire the male patients obtained scores consistently reflecting a greater degree of illness than that revealed in the scores of the female patients.

As a result of these findings and considerations, we are restricting our comments on the outcome of the statistical analysis to the findings obtained only from the 31 females included in this trial. For these patients no significant differences were found between active and placebo treatments in comparison with pre-trial level on the tests of vocabulary or memory or on the psychiatric questionnaire. Significant differences in favour of the active treatment were found, however, on the tests of intelligence (P<0.01) and on the Raven's Coloured Progressive Matrices (P<0.05), whilst the benefits of active over placebo treatment on the Paired-Associate Learning Task fall just short of acceptable level of statistical significance (P<0.075).

DISCUSSION

In this study of apparently normal elderly people living in their homes and functioning in the community, significant improvement in some aspects of mental function has been described under stringent double-blind cross-over trial techniques in females. Unfortunately males in this series suffered progressive intellectual and behavioural impairment. We have no real explanation as to why the males and females differed so significantly. One possibility must centre on the selection procedure employed, for whilst the intention of the investigators was to obtain an unselected sample of patients, nevertheless the total sample contained a large number of husbands and wives. There is a possibility of bias in this, for the wives appeared to have been mentally more healthy than their spouses, and their possible anxiety regarding their husbands may have led to pressure by the wife for both partners to participate.

In so far as the female subjects are concerned we would place particular stress on the improvement of 'intelligence', which is evident in this trial since until now deterioration of 'intelligence' has been regarded by some authorities as a physiological component of
the ageing process. Its reversal by a drug throws doubt on this concept and the practical implications are enormous.

Finally we would like to speculate about the early treatment of patients who are believed to be suffering from some minor cerebrovascular disorder. They may be the most appropriate cases for treatment with cyclandelate. In this respect, we are in agreement with Birkett (1971), who has also stressed the importance of early treatment in cases of cerebral vascular disorders if drug therapy is to be of any value.

ACKNOWLEDGEMENTS

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REFERENCES


