Effect of Cyclandelate on Dementia

BY GILBERT WESTREICH, M.D., MILTON ALTER, M.D., PH.D., AND SANDRA LUNDGREN, PH.D.

Abstract:
Cyclandelate, a vasodilator, was administered to 24 patients with dementia. The dementia in these patients was presumed to be due to cerebral ischemia caused by atherosclerosis in cerebral vessels after other possible causes were ruled out. In a double-blind, cross-over study, patients received 200 mg of cyclandelate four times daily for six weeks and a placebo for six weeks. Six psychological tests, which reflect various aspects of higher cortical ability, were used to evaluate the effect of cyclandelate on the dementia. Cyclandelate was found to be no more effective than placebo in improving higher cortical function in these demented patients.

Additional Key Words
mental function
vasodilator
cerebral arteriosclerosis

Physiological research has shown cyclandelate to be effective in causing vasodilation of the arteries of the skull and brain in geriatric patients and to increase cerebral cortical perfusion in patients with cerebrovascular disease. Cyclandelate has been shown to raise the volume of blood circulated and reduce circulation time in patients with cerebrovascular insufficiency. It also has been reported that cyclandelate decreases the number of recurrences of transient cerebral vascular attacks.

This effect on cerebral circulation has raised the possibility that cyclandelate also may be effective in treating some types of dementia. The dementias have a heterogenous etiology but a proportion are believed to be due to cerebral ischemia caused by atherosclerosis in cerebral vessels. A vasodilator, such as cyclandelate, could conceivably improve cerebrovascular perfusion by affecting vessels which are not, as yet, too sclerotic to dilate.

Recent behavioral studies, however, have not been consistent in demonstrating a beneficial effect of cyclandelate on higher cortical brain function. In one study, elderly patients on cyclandelate showed significant improvement in mental functioning, but there was no significant correlation between the changes in a patient’s score on the mental function tests and changes in mean circulation. In addition, the psychological test measurements employed in that study have been criticized as being too imprecise. In another study, patients with moderate atherosclerosis showed significant improvement on four of nine measures (three subtests of the Wechsler Intelligence Scales and the Raven Coloured Progressive Matrices) considered to be sensitive to change in cortical brain function. In a more rigorous study with a double-blind, cross-over design, the results were equivocal and it was concluded that further experimental verification was required.

The present study of cyclandelate was also of the double-blind, cross-over type. This design, in which each patient serves as his own control, has the advantage of minimizing the effect of individual differences on the assessment of benefit. If cyclandelate were effective, dementia after six weeks on the drug should be significantly less than during the pretrial period and after six weeks on placebo.

Methods

Subjects
The patients were all male veteran inpatients on the Neurology Service of the Minneapolis Veterans Administration Hospital. Thirty-one patients were admitted to the study. Of these, two patients were eliminated because of questionable histories of chronic alcoholism, two patients refused to complete the study, two died before the completion of the study, and one was terminated after a rash developed. Thus, 24 patients contributed analyzable data. These patients ranged in age from 51 to 82 years (mean 70.8 years).

Procedure
All patients admitted to the Neurology Service with a diagnosis compatible with dementia were first screened medically. Baseline medical status for a variety of categories was established using the battery shown in table 1. Patients with various illnesses likely to preclude completion of the study, such as carcinoma, severe lung disease or severe cardiac insufficiency, were identified in the medical screening and excluded. Patients with medical complications of chronic alcoholism or dementia so far advanced as to preclude participation also were eliminated. Thus, patients included in the study were essentially normal on all the tests.
of the medical screening battery. Patients who received medication other than cyclandelate, such as vitamins and tranquillizers, continued to receive these drugs at constant dosages during both the placebo and cyclandelate phases of the study. Patients received no other vasodilating drugs.

Informed consent of the patient or, more often, a responsible relative was obtained. Patients were randomly allocated to one of two groups. Group 1 received cyclandelate first for six weeks, followed by placebo for another six weeks. Group 2 received placebo first, then cyclandelate. The code was maintained by the hospital pharmacist and was unknown to either the clinicians or the patients. Cyclandelate was given in an oral capsule of 200 mg four times daily. Daily records of capsule administration were maintained by the nursing staff to assure that the patients received the full dose. The patients remained in the

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**TABLE 1**

**Medical Screening Battery**

<table>
<thead>
<tr>
<th>Category</th>
<th>Specific measures</th>
</tr>
</thead>
</table>
| A. General physical condition and pertinent medical history | 1. Height  
2. Weight  
3. Previous serious illnesses  
4. Previous operations  
5. Previous long-term medications  
6. Smoking history (average number of cigarettes/day; pack years)  
7. Alcoholic beverage history (average cc/week)  
8. Visual acuity  
9. Auditory acuity  
10. Serology for syphilis  |
| B. Cardiovascular status                | 1. EKG — on day of admission, pulse  
2. Blood pressure t.i.d. x 3 days  
   | Average Range  
   | Systolic          
   | High systolic — low systolic  
   | Diastolic          
   | High diastolic — low diastolic  |
| C. Pulmonary status                     | 1. Chest x-ray  
2. Tidal volume  |
| D. Neurological status                  | Clinical  
   | 1. Cranial nerves  
   | 2. Motor system  
   | 3. Reflexes  
   | 4. Sensation  
   | 5. Coordination  |
| E. Metabolic status                     | Laborator  
   | 1. Cholesterol  
2. Calcium  
3. Phosphorus  
4. Bilirubin total  
5. Albumin  
6. Total protein  
7. Uric acid  
8. Urea nitrogen  
9. Glucose  
10. LDH  
11. Alkaline phosphatase  
12. SGOT  
13. Electrolytes — Na, K, CO₂, Cl  
14. Two-hour postprandial blood sugar  |

*Procedure done for some patients only.
EFFECT OF CYCLANDELATE ON DEMENTIA

Table 1

Psychometric Tests

<table>
<thead>
<tr>
<th>Parameter of mentation</th>
<th>Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Visual spatial perception</td>
<td>Bender Visual Motor Gestalt Test</td>
</tr>
<tr>
<td></td>
<td>Graham-Kendall Memory-For-Designs Test</td>
</tr>
<tr>
<td>B. Memory</td>
<td>Wechsler Memory Scale</td>
</tr>
<tr>
<td></td>
<td>Benton Visual Retention Test</td>
</tr>
<tr>
<td>C. Intelligence</td>
<td>Wechsler Adult Intelligence Scale</td>
</tr>
<tr>
<td>D. Logical thinking</td>
<td>Raven Coloured Progressive Matrices</td>
</tr>
</tbody>
</table>

hospital throughout the study except for an occasional weekend pass, during which capsules were administered by a responsible family member.

All patients were given identical programs in occupational, recreational and physical therapy. The clinical condition of each patient was rated biweekly by a nurse and a physician. Various aspects of higher cortical function were evaluated using the battery of tests shown in Table 2. These tests were given on admission to the study, repeated after six weeks, and again at 12 weeks.

Results

Table 3 shows the average pretrial scores for both groups on each of the psychological tests and the average scores after six weeks and after 12 weeks. Comparisons of baseline performance revealed no significant difference between Group 1 and Group 2 on any of the tests, indicating that the two groups were comparable in higher cortical functions. Moreover, the test scores provide objective confirmation of the clinical diagnosis of moderate dementia in these patients. For example, patients made about 20 errors on the Graham-Kendall Memory-for-Designs Test. A score of 12 or more errors on this test is accepted as an indication of impaired cerebral function. In addition, the patients in the present study fell into the “dull normal” category for verbal IQ and into the “borderline” category for performance IQ on the Wechsler Adult Intelligence Scale (WAIS). On the Raven Coloured Progressive Matrices, these patients also performed at a “definitely below average” intellectual capacity. Although significantly impaired on these tests, the patients were not so severely demented that they fell into the lowest category as mentally or intellectually defective. As indicated by the Wechsler Memory Scale, however, memory function was quite severely impaired in these patients. The poor performance and memory disability also were apparent on the Bender Visual Motor Gestalt Test and the Benton Visual Retention Test. Patients were able to reproduce only about one of the eight and ten drawings, respectively, in these tests.

The changes in performance at six weeks and 12 weeks included not only the anticipated effect of treatment but also a possible general beneficial effect of the hospital environment and the occupational and physical therapy programs. Statistical analyses, using standard \( t \) tests, were carried out to evaluate the significance of these effects, as well as the drug effect, on each of the psychological tests. One analysis (Bender-Gestalt, number recalled) revealed significant (\( P < 0.05 \)) improvement over time for both the cyclandelate and the placebo phases, i.e., both groups were able to recall more at 12 weeks than initially or at six weeks (table 3). Only scores on the Wechsler Memory Scale (MQ) and the WAIS full scale IQ changed significantly (\( P < 0.05 \)) during the study as a

Table 3

Mean Raw Scores of Pretrial, Six-Week and 12-Week Periods

<table>
<thead>
<tr>
<th>Test</th>
<th>Group 1 (Drug—placebo)</th>
<th>Group 2 (Placebo—drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretrial</td>
<td>6-week</td>
</tr>
<tr>
<td>Bender-Gestalt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct</td>
<td>0.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Number recalled*</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Graham-Kendall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number errors</td>
<td>19.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Wechsler Memory Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MQ</td>
<td>64.6</td>
<td>66.5</td>
</tr>
<tr>
<td>Wechsler Adult Intelligence Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(WAIS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>92.0</td>
<td>92.0</td>
</tr>
<tr>
<td>Performance IQ</td>
<td>80.3</td>
<td>82.4</td>
</tr>
<tr>
<td>Full scale IQ*</td>
<td>89.0</td>
<td>89.6</td>
</tr>
<tr>
<td>Benton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Number errors</td>
<td>23.0</td>
<td>23.7</td>
</tr>
<tr>
<td>Raven Coloured Progressive Matrices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number correct</td>
<td>12.2</td>
<td>13.7</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \).
result of treatment but, as shown by table 3, MQ improved more during the placebo period than during the cyclandelate period for both groups and the change in full scale IQ is attributable to an improvement only for Group 2 during the placebo period. Thus, the results appear to indicate that, for the demented patients in this study, cyclandelate was no more effective than placebo in improving higher cortical function.

Discussion

To our knowledge, there have been only four previous double-blind, cross-over evaluations of cyclandelate.7-10 The results of the present study are essentially in agreement with the results of those studies. Aderman and his associates7 studied the effects of cyclandelate in two groups of geriatric subjects, analogous to the groups in the present study, using six psychological tests. Of these tests, four were identical to or subtests of those we used. In both our study and the Aderman et al. study, these four tests revealed that cyclandelate had no significant beneficial effect. Although the other two tests used by Aderman et al. showed significant improvement, one group improved on one test only and the other group improved on the second test.

Judge et al.14 assessed mental function in normal elderly male and female patients, again with a battery of six tests. It was found that only the female patients contributed analyzable data. For these female patients, only two of the six measures showed significant differences in favor of cyclandelate. These two measures were the Raven Coloured Progressive Matrices and an abbreviated intelligence test. In the present study and the Aderman et al. study, however, the Raven Matrices and other measures of intelligence did not show any significant change in favor of cyclandelate.

In the study by Young et al.,15 patients with objective signs of dementia and cerebral arteriosclerosis were given cyclandelate and placebo. Patients did not improve while on cyclandelate. Rather, during the course of the study, patients declined on various measures of neurological, behavioral and psychometric parameters. It was observed, however, that the decline was greater during the placebo phase than during the cyclandelate phase. No such decline during the course of the trial was noted in the present study, possibly because the patients in the present study began at a lower pretrial level than in the Young et al.15 study. Patients in that study actually began with an “average” IQ. The results of the Young et al. study suggest that cyclandelate may slow the progression of dementia if administered in the very early stages of the disease. However, in the present study of patients with a moderate degree of dementia, cyclandelate was found to be no more effective than placebo in improving higher cortical function. In Fine’s14 study, among nine measures compared, the only measure in which sustained improvement occurred on the drug was “orientation.”

It should be realized that patients in the present study were presumed, by a process of exclusion, to have dementia due to cerebral arteriosclerosis, a clinical entity which is not universally accepted.13 It is possible that some other process (e.g., primary neuronal degeneration) was responsible for the dementia in these patients. If this were the case, cyclandelate, or any other vasodilator, would not be expected to be an effective treatment.

Acknowledgment

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