CLINICAL AND RESEARCH REPORTS

This section contains 1) new research findings, including preliminary data from pilot studies, either clinical or laboratory; 2) worthwhile replication studies; 3) case reports that describe a truly new syndrome or cast new light on established ones; and 4) case reports that indicate a new therapeutic procedure of potential value or call attention to adverse effects of drugs or previously unreported complications of therapeutic interventions. Program descriptions and literature reviews cannot be printed in this section. Criteria for format are listed in "Information for Contributors" in each issue; papers that do not adhere to these criteria will be returned to the author.

Physostigmine and Its Effect on Six Patients with Dementia

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Many authors have suggested that acetylcholine agonists might improve memory in patients with dementia of Alzheimer type. This idea is based on the association between acetylcholine and human memory (1), especially the findings that cholinomimetics improve memory in young, normal volunteers (2, 3) and that autopsies on subjects who had dementia of Alzheimer type showed a reduction in choline acetyltransferase, which is indicative of a central cholinergic deficit (4, 5). Previous investigators who used physostigmine (6), choline (7), or lecithin (8) in their studies found little or no memory enhancement in demented patients. We now report that when intravenous physostigmine, a short-acting central anticholinesterase, was used in a double-blind single, acute trial, it failed to improve the memory of six patients with dementia of Alzheimer type as measured by a modified Buschke Word List Learning Test or a modified Benton Visual Retention Test.

Method

Patients for this study were recruited from the inpatient population of the UCLA geriatric neuropsychiatry unit. Prospective patients were diagnosed on the basis of neurologic, psychiatric, and other medical evaluations, including EEGs and cerebral CT scans. We selected six patients (five women and one man) who were diagnosed as having dementia of Alzheimer type. They ranged in age from 59 to 81 years and had an average of 4–13 years of education. These patients met *DSM-III* criteria for primary degenerative dementia: 1) dementia was a core clinical feature, 2) onset was insidious and there was progressive deterioration, and 3) other specific causes of dementia were excluded. The dementia was marked by cognitive dysfunction (e.g., none was oriented to date) and memory impairment (e.g., none was able to recall any of five objects 5 min after presentation). All patients were ambulatory although none was able to live independently. No patient with significant cardiac disease was included. Every participant gave oral and written consent, as did a relative or other appropriate person.

Each patient was given .5 mg of physostigmine in water (drug) on one day and dextrose in water (placebo) on another day. For each patient testing days were nonconsecutive. The order of days (drug-placebo or placebo-drug) was counterbalanced across the patient group and chosen in a double-blind fashion; only the hospital pharmacy knew the order while the subjects were being tested. On a testing day the agent, drug or placebo, was administered by constant intravenous infusion (by IVAC) over 30 min. After 20 min of infusion, the neuropsychologist (J.S.) began the testing. First, a modified Buschke Word List Learning Test was administered. One list of 10 words was read to the patient six times, and immediately after each reading the number of words the patient correctly

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repeated, regardless of order, was recorded and totaled. At the end of the infusion each patient was given a modified Benton Visual Retention Test. After viewing a stimulus card for 10 sec the patient drew the stimulus design from memory. Five stimulus cards were shown, each more difficult than the one preceding.

Two equivalent forms of each memory test were presented to each patient because repetition of an identical test, even 2 or more days later, might affect performance. To avoid drug-placebo sequence and test form interactions, each form was given first in an equal number of drug-placebo and placebo-drug sets; one form of each test was given first four times and the other twice. The order of these equivalent forms was also specified beforehand by the hospital pharmacy.

Results

The patient's mean score on the modified Buschke Word List Learning Test after they had received physostigmine was 19.2; after they had received placebo their mean score was 17.8 (not significant). However, when we compared the highest correct responses (the most words out of 10 sample words that a subject could recall over six presentation-response trials) obtained by each of the six patients (6,4,3,5,5,4 while taking physostigmine and 5,6,4,4,8,2 while on placebo), a linear regression analysis over each patient's block of six trials under each condition showed a trend toward poorer verbal retention and less improvement on trials after the patients had received physostigmine.

For the modified Benton Visual Retention Test there was no significant difference between the patients' correct responses after they had taken physostigmine (3,0,1,0,0,1) and after they had received placebo (4,1,0,0,3,0) although there was a trend toward poorer visual retention after they had received physostigmine.

No serious side effects or ECG changes were noted. One patient experienced nausea, which was attributed to the physostigmine.

Discussion

Intravenous physostigmine, administered in the low-dose range reported to have a beneficial effect on memory in younger normal individuals (2), did not improve learning or memory, as measured by two specific memory tests, in older patients who were moderately to severely demented. Agents that enhance central cholinergic activity can be expected to also enhance the functioning of only those neuronal circuits involved in memory processing that use acetylcholine as a neurotransmitter (presumably in the hippocampus [1]) and not of those circuits that have already been disrupted by Alzheimer-type degeneration (9). For this reason physostigmine may be beneficial only if 1) the dose is titrated individually (6), 2) more sensitive and specific memory tests than those used here are included (6), 3) the drug is given in conjunction with lecithin (10), and 4) it is administered only to individuals with mild memory impairment (10).

This study rules out neither an acute beneficial effect of physostigmine nor a potentially beneficial effect of the chronic administration of a cholinergic agonist alone or in combination with other agents (e.g., a central noradrenergic agonist). It does point out, however, that such studies need to be carefully designed and meticulously controlled. The prevalence of dementia of Alzheimer type demands that more scientific investigations explore the etiology and treatment of this tragic illness.

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