Intern. J. Neuroscience, 1983, Vol. 18, pp. 143–148
0020-7454/83/1802-0143$18.50/0

ACUTE ADMINISTRATION OF INDIVIDUAL OPTIMAL DOSE OF PHYSOSTIGMINE FAILS TO IMPROVE MNESIC PERFORMANCES IN ALZHEIMERS PRESENILE DEMENTIA

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(*Received August* 2, 1982)

Eight patients affected by Alzheimer's Presenile Dementia (AD) received acute administration of physostigmine individual optimal dose per os ($n = 4$) or subcutaneously ($n = 4$). The individual physostigmine dose was assessed by means of serum cholinesterase activity monitoring. The possible beneficial effects after treatment were evaluated by using two memory tests: Reys' 15 words and Digit Span from Wechsler memory scale. Although a slight behavioral activation was noted in all patients after treatment, the comparison between mean scores obtained by AD patients in mnesic tests before and after the acute physostigmine administration, with either therapeutic modality, failed to reach the level of statistical significance. Some implications of these disappointing results are briefly discussed.

The evidence of early memory impairment in Alzheimer's Presenile Dementia (AD) has been recently related to a selective deficit of the cerebral cholinergic system (Davies & Maloney, 1976; Perry *et al.*, 1977). Furthermore, experimental data in animals (Barthus, 1978 and 1979), in normal humans (Davis *et al.*, 1978) and in normal elderly subjects (Drachmann, 1980) suggested that learning and memory tests are modified by drugs active on cholinergic system.

On this basis, many therapeutic attempts have been made by several authors to improve mnesic performances in AD patients by using cholinergic agents. Physostigmine seems to determine favourable changes more than other cholinergic drugs. This is true especially when treatment is administered at the beginning of the disease, that is when dementia is not very advanced (Glen & Whalley, 1979). We recently reported (Caltagirone *et al.*, 1982) that chronic oral administration of physostigmine does not improve cognitive and mnesic performances in AD. However, our negative results might be due to a different individual reactivity to an identical dose of physostigmine. In fact, the response to anticholinesterase agents displays a definite individual variability; this is also the case with physostigmine, for which the controversial results quoted by different authors may be due to the difficulty in determining an 'individual optimal dose' (Zeisel *et al.*, 1981).

In order to assess this physostigmine dose, the simplest method we found has been serum cholinesterase monitoring. We hypothesized that a physostigmine dose capable of reducing in the single patient serum cholinesterase levels, had better chances of improving memory performances than a dose identical for all patients. The present study was aimed at evaluating whether acute administration of an individual optimal dose of physostigmine improves memory performances in AD.

Methods

Our sample was formed by eight patients with history of progressive dysmnesia. Particular care was taken in selecting patients affected by an initial form of intellectual

deterioration. In fact, the mean duration of the symptoms was 1.5 years and the degree of dementia was so slight that it did not prevent patients from living at home, not supported by their relatives. On the other hand, performances obtained on a neuropsychological Mental Deterioration Battery revealed only a slight cognitive impairment in addition to the memory dysfunction.

On the basis of clinical, neuroradiological and neuropsychological data they were diagnosed as suffering from AD (Table 1). The patients were randomly assigned to two different groups: one ($n = 4$) received oral physostigmine, while the other group ($n = 4$) was given the drug subcutaneously. In order to prevent peripheral cholinergic symptoms, all patients received, 45 min before treatment, homatropine methylbromide —an anticholinergic agent which does not across the blood-brain barrier—in a single dose of 7.5 mg per os. In all patients serum cholinesterase activity was monitored before and after treatment.

Cholinesterase determination. Cholinesterase was measured spectrophotometrically in serum obtained from blood samples, according to the technique described by Rappaport et al. (1959). Acetylcholine chloride was used as a substrate; acetylcholinesterase activity was quantified as micromoles of acetic acid produced from the substrate in the presence of n-nitrophenol as indicator.

Oral administration. Each patient in this group received an initial dose of 2 mg of physostigmine per os. Blood samples were drawn before ingestion and 30 and 60 min later. Serum cholinesterase activity in the two samples obtained after drug administration was compared to the pretreatment value. In subsequent sessions the drug was gradually increased 1 mg at a time, until the optimal individual dose was reached. Individual optimal dose was defined as the dose capable of reducing cholinesterase activity by at least 15%. In fact, when a higher reduction was obtained, the patients displayed such a marked evidence of cholinergic side effects that retesting was prevented in spite of anticholinergic pretreatment.

Subcutaneous administration. In this group each patient received an initial dose of 0.5 mg of physostigmine s.c. Blood samples, drawn before the injection and 15, 30 and 45 min later, were compared as described for the oral administration. In the following sessions the dose was gradually increased by 0.1 mg at a time, until the optimal individual dose (defined as above) was reached.

Memory assessment. Mnestic performances were evaluated by means of Reys' 15 words (Rey, 1958) and digit span from Wechsler Memory Scale. These tests were

TABLE 1

Criteria used for the diagnosis of Alzheimer's Disease

1– History of chronic and progressive deterioration of intellectual functions with dysmnesia as the initial feature.

2– Absence of important risk factor or evidence of cerebrovascular disease.

3– Absence of focal neurological signs and symptoms.

4– Hachinski's ischemia score not exceeding the level of 4.

5– CT scan showing a diffuse and roughly symmetrical brain atrophy.

given before treatment to identify basal individual performances. Then parallel forms of the tests were repeated, in every session, 45 min after oral physostigmine or 25 min after subcutaneous administration. Thus, in the two different settings, memory testing took place at different intervals from the drug administration because individual monitoring showed that decrease of serum cholinesterase activity reached its peak 45 min after oral administration and 25 min after physostigmine s.c.

Results

As indicated in Table 2, the mean values of individual optimal dose of physostigmine in the two different therapeutic settings were quite different. The mean dose for the oral administration was 3.75 mg ($\pm$ 0.85), while for the subcutaneous administration 0.75 mg ($\pm$ 0.05) were used. Although the physostigmine doses were relatively high, none of our patients demonstrated cholinergic side effects when given the optimal dose, probably because they were pretreated with homatropine methylbromide. Doses of physostigmine higher than the ones reported above, produced, even in the presence of anticholinergic pretreatment, relevant cholinergic side effects which prevented re-testing. When the individual optimal dose was administered, either orally or subcutaneously, all patients showed only slight behavioral modifications consisting of increased arousal, alertness and responsiveness to the environment. However, the comparison between mean scores obtained by AD patients in mnesic tests before and after acute physostigmine, with either therapeutic modality, failed to reach the level of statistical significance (Table 2).

Discussions

The results of the present study are disappointing. In fact, our data show that even an acute optimal dose of physostigmine does not improve mnesic performances in AD.

TABLE 2

Mean values of memory performance scores obtained by AD patients before and after acute oral or subcutaneous physostigmine. Mean values of individual physostigmine optimal dose in the two different experimental settings are indicated

	Before treatment	After treatment
	$\bar{x}$ (*S.D.*)	$\bar{x}$ (*S.D.*)
Oral administration ($N = 4$)		
individual optimal dose of physostigmine: $\bar{x} = 3.75$ mg		
— Rey's 15 words — short term	16.0 (5.1)	19.5 (8.1)
— Rey's 15 words — long term	2.0 (0.8)	2.0 (0.8)
— Digit span	4.7 (1.2)	5.0 (1.4)
Subcutaneous administration ($N = 4$)		
individual optimal dose of physostigmine: $\bar{x} = 0.75$ mg		
— Rey's 15 words — short term	14.7 (2.1)	14.0 (2.2)
— Rey's 15 words — long term	2.3 (1.2)	1.0 (0.7)
— Digit span	4.3 (0.7)	5.3 (0.9)

Oral and subcutaneous roots are equally ineffective. However, the acute administration of physostigmine at this optimal individual dose confirms our previous indications (obtained after chronic oral administration of the same drug at lower dosages) that a slight behavioral activation can be observed in AD after cholinergic therapy (Caltagirone at al., 1982). Thus, our data seem to support Corkin's statement (1981) "yet there is no overwhelming evidence . . . that (in AD) treatments which enchance central cholinergic neurotrasmission should be effective therapy."

This doubtful effectiveness of cholinergic treatment in AD can be traced to one of the following reasons:

(a) an inconsistent therapeutic activity of physostigmine;
(b) a nonselectivity of cholinergic impairment in AD;
(c) methodological reasons.

As for the first point, Alderdice (1979) demonstrated that, at peripheral level, there is evidence for an inhibitory action of physostigmine on the acetylcholine release. If this additional action of physostigmine was shown to occur in the central nervous system too, this contrasting effect between inhibition of the release of acetylcholine and of cholinesterase activity, could explain the inconsistent clinical findings obtained with this drug. Evidently, it would depend on which action of physostigmine (cholinesterase inhibition or transmitter release inhibition) is more pronounced. As for the second point, Mann and coworkers (1982) claimed that, in AD, there is a severe loss of the noradrenaline containing pigmental neurons of the locus coeruleus and vagus nucleus together with decrease in the protein synthetic activity of remaining cells. On the other hand, biochemical studies had shown that decreased levels of homovanillic acid can be demonstrated in the neostriatum and in CFS of patients affected by AD (Gottfries *et al.*, 1969a; Gottfries *et al.*, 1969)b. Then the decreased activity of CAT could be only one of the aspects of neurotrasmission impairment in AD. Finally, as for the methodological reasons, it is possible that neuropsychological tasks (and in particular memory tests) are too demanding to reveal improvement following cholinergic therapy in AD. A more fruitful approach could consist perhaps, of using behavioral scales in addition to the more objective memory tests to demonstrate possible improvement in these patients.

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