Short report

Bethanechol decreases reaction time in senile dementia of the Alzheimer type

P DAVOUS,* Y LAMOUR†

From the Department of Neurology, Cochin Port-Royal Medical School, and INSERM U161,† Paris, France*

SUMMARY Bethanechol, a muscarinic cholinergic agonist, was injected subcutaneously in eight cases of senile dementia of the Alzheimer type. Simple reaction time was measured before, 15 min and 30 min following the injection. Before injection, the patients had significantly longer reaction time than non-demented controls. A significant shortening of the reaction time was observed 15 min but not 30 min after injection. A second group of eight patients with senile dementia of the Alzheimer type, matched for age and mental impairment were injected with saline. No significant shortening of the reaction time was observed. These results suggest that the reaction time can be shortened by a muscarinic agonist in dementia of the Alzheimer type.

Alzheimer's disease and, more generally, senile dementia of the Alzheimer type are characterised by a relatively specific central cholinergic deficit.¹ Many attempts to improve the cognitive functions in Alzheimer type dementia by acetylcholine precursors failed to show a significant benefit. Nevertheless, some improvement in memory has been obtained after administration of cholinergic drugs, specially physostigmine.²

Bethanechol is a muscarinic agonist with excitatory properties when applied on cortical or hippocampal neurons by iontophoresis.^{3,4} Though not crossing easily the blood-brain barrier, it is not destroyed by cholinesterase and has central effects when administered at the periphery (Lamour, unpublished observations), as do some other structurally related quaternary ammonium compounds such as muscarine and acetylcholine.

Methods

We studied 16 patients with Alzheimer type dementia, 10 males and six females. In each case, the diagnosis was based on DSM III criteria,⁵ Hachinski score,⁶ normal metabolic and spinal fluid studies and CT scan showing diffuse cerebral atrophy. Alzheimer patients or their relatives gave informed consent for the trial. Patients were non randomly assigned to two different groups. Those in the

first group (group I) received an initial subcutaneous injection of 0.25 mg methylscopolamine (an antagonist of the peripheral effects of muscarinic drugs, not crossing the blood-brain barrier) and 5 minutes later a second subcutaneous injection of 0.1 mg/kg of bethanechol (Urecholine, Merck Sharp and Dohme). Patients in the second group (group II) received 1 ml of saline. Patients in both groups were matched for age (mean $\pm$ SEM: 65.4 ± 3.9 in group I, range 46–80 and 69.1 ± 2.3 in group II, range 60–79). They were also matched for the level of deterioration as assessed by the mental status questionnaire (MSQ) score⁷: mean $\pm$ SEM in group I: 6.5 ± 0.9 , range 3–10 and in group II: 7.3 ± 0.8 , range 5–10.

The task was a simple reaction time paradigm. The subjects were asked to depress a switch with their index finger, as fast as possible, when a red light located near the switch was turned on. The light was turned on at random intervals of time. The switch was connected to an electronic clock (Rochar A926). After ten practice trials, the reaction time was measured for 20 additional trials. The mean reaction time was calculated from these 20 trials. Three consecutive series of trials were administered: the first prior to any injection, the second 15 minutes and the third 30 minutes following the injection of bethanechol or saline. The occurrence of side effects was carefully checked. In group I, the most common side effects were micturition and in two cases only, abdominal cramps. Heart rate and blood pressure (monitored every 5 minutes) were not significantly modified by bethanechol injections. In group II no side effect was observed.

Results

In a preliminary study, the simple reaction time (RT) was measured in 54 normal subjects, in two classes of age: in the first group (range of age 20–49,

Address for reprint requests: P Davous, Service de Neurologie, Hôpital Sainte-Anne, 1 rue Cabanis, 75674 PARIS CEDEX 14, France.

Received 30 November 1984 and in revised form 26 April 1985.
Accepted 10 May 1985

$n = 30$), the mean $\pm$ SEM reaction time value was 247 ± 7 ms. In the second group (range of age 50–94, $n = 24$), the mean $\pm$ SEM value was 314 ± 17 ms. We also measured simple reaction time in non demented Parkinsonian patients ($n = 10$, mean age 68 ± 2.3 , MSQ = 9.7 ± 0.2). The mean $\pm$ SEM reaction time was 370 ± 33 ms. These values are in agreement with those previously published for normal and Parkinsonian subjects.⁸

Under the same experimental conditions, the mean $\pm$ SEM reaction time value of Alzheimer type dementia patients was 776 ± 136 ms ($n = 16$). The difference with normal subjects is statistically significant ($p < 0.001$, Student's t test). These results confirm that patients with Alzheimer type dementia have longer reaction time than normal subjects of similar age.⁹ They also show that there are much larger variations in reaction time in Alzheimer type dementia patients than in normal subjects or even in Parkinsonian patients.

The results in Alzheimer type dementia patients are summarised in tables 1 and 2. The mean $\pm$ SEM reaction time values prior to injection in groups I and II were respectively 822 ± 228 ms ($n = 8$) and 729 ± 162 ms ($n = 8$). They were not significantly different (Student's t test).

In group I, we observed a significant shortening of the reaction time 15 minutes following bethanechol injection, as compared to the pre-drug values ($p < 0.01$, Wilcoxon matched pairs test). Thirty minutes following injection, the values returned to or close to the pre-drug values. The difference between 15 minutes and 30 minutes reaction time was significant

($p < 0.05$). In all individual cases but one (group I), the 15 minutes reaction time was shorter than the pre-drug reaction time. The mean percentage of shortening was 15.8% as compared to pre-drug values (range 10–31%). Thirty minutes following drug injection reaction time was longer than at 15 minutes (mean lengthening: 18.5%, range 2.6–42%). There was no significant difference between pre-drug and 30 minutes reaction time values.

In group II there was no significant shortening of the reaction time: four patients had a shorter individual mean reaction time 15 minutes following saline injection, whereas in four cases the individual mean reaction time was longer. The shortening of the individual mean reaction time was extremely small in three cases out of four. The mean change was actually a 13.3% lengthening of reaction time. In most of the cases (five out of eight), the thirty minutes reaction time (in group II) were longer than the fifteen minutes reaction time. The mean difference was however of only 3.3%. These values were 16.1% longer than the control values.

The only side effect observed in group I patients was micturition (all patients), usually occurring between the second and the third series of trials. Abdominal cramps were observed in two patients. These side effects did not disturb the experimental sessions.

Discussion

Our results provide evidence that the reaction time of Alzheimer type dementia patients is shortened by prior injection of the muscarinic agonist

Table 1 Reaction Time (mean $\pm$ SEM) in Alzheimer type dementia patients (Group I) before and after bethanechol injection

	Sex	Age	T_0	D%	T_{15}	D%	T_{30}	D%	MSQ
1	M	70	1037 ± 175	(-18.3)	847 ± 172	(+42)	1204 ± 174	(+16.1)	3
2	M	69	824 ± 40	(-12.9)	717 ± 51	(+22.5)	879 ± 80	(+6.6)	8
3	F	66	624 ± 55	(-31)	426 ± 32		R		6
4	F	74	606 ± 27	(-22.2)	471 ± 24	(+21.4)	572 ± 68	(-5.6)	7
5	M	53	414 ± 34	(+5.5)	437 ± 43	(-13.5)	378 ± 28	(-8.6)	3
6	M	80	413 ± 36	(-26.1)	305 ± 17	(+2.6)	313 ± 14	(-24.2)	10
7	M	65	2318 ± 175	(-11.5)	2050 ± 131	(+41.7)	2906 ± 305	(+25.3)	5
8	M	46	340 ± 17	(-10.2)	305 ± 9	(+13.1)	345 ± 20	(+1.4)	10
Means 65.4 ± 3.9			822 ± 228	(-15.8)	.01*	(+18.5)	.05†	(+1.5)	6.5 $\pm$ 0.9
NS‡									

T indicates the mean RT values for each patient prior (T_0) 15 minutes (T_{15}) and 30 minutes (T_{30}) following bethanechol (Table 1) or saline (Table 2) injection. D% indicates the differences (in percent) between T_0 - T_{15} , T_{15} - T_{30} and T_0 - T_{30} respectively (from the left to the right). Mean differences are given at the bottom of each table. Degrees of significance are indicated, according to the Wilcoxon matched pairs test. (R: refused retest) (MSQ: Mental status questionnaire). (*compared with T_0 , †compared with T_{15} , ‡compared with T_{30}).

Table 2 Reaction Time (mean $\pm$ SEM) in Alzheimer type dementia patients (Group II) before and after saline injection

	Sex	Age	T ₀	D%	T ₁₅	D%	T ₃₀	D%	MSQ
1	F	60	1343 $\pm$ 81	(-0.7)	1333 $\pm$ 108	(+0.2)	1336 $\pm$ 76	(-0.5)	7
2	M	63	285 $\pm$ 26	(-1.4)	281 $\pm$ 15	(+2.8)	289 $\pm$ 17	(+1.4)	10
3	M	67	595 $\pm$ 34	(+9.9)	654 $\pm$ 41	(+12.2)	734 $\pm$ 47	(+23.3)	6
4	M	72	912 $\pm$ 70	(+10)	1004 $\pm$ 73	(-14.6)	857 $\pm$ 70	(-6)	5
5	F	75	484 $\pm$ 28	(-2.8)	470 $\pm$ 25	(-15.9)	395 $\pm$ 30	(-18.3)	10
6	F	73	406 $\pm$ 26	(+55.4)	631 $\pm$ 57	(-2)	618 $\pm$ 65	(+52.2)	5
7	F	79	1457 $\pm$ 161	(-17.2)	1205 $\pm$ 114	(+38.4)	1668 $\pm$ 185	(+14.4)	6
8	M	64	352 $\pm$ 18	(+53.6)	541 $\pm$ 39	(+5.9)	573 $\pm$ 46	(+62.7)	10
Means 69.1 $\pm$ 2.3			729 $\pm$ 162	(+13.3)		(+3.3)		(+16.1)	7.3 $\pm$ 0.8
NS*									
NS†									
NS‡									

See footnote to table 1.

bethanechol. This shortening is not due to learning since it was not observed in Alzheimer type dementia patients performing the same task but receiving only saline (table 2).

One might suggest that the shortening of the reaction time is due to an indirect effect, namely the effect of bethanechol on peripheral and not central muscarinic receptors, being responsible for an arousal reaction via indirect stimulation of visceral receptors. However, this explanation seems unlikely, since the peripheral effects of the drug were usually limited to micturition and most of the patients were indifferent to it and did not report any painful sensation. Therefore, it is likely that the shortening of the reaction time is due to the central effect of the drug. Preliminary results of long term oral¹⁰ and of ventricular¹⁰ administration of bethanechol seem to support this hypothesis.

The marked variation in reaction time values observed between and within Alzheimer type dementia patients seems to be a feature of dementia since it was not observed in normal subjects or Parkinsonian patients. Furthermore, the lengthening of the reaction time in Alzheimer type dementia patients was positively correlated with the severity of the deterioration (P Davous, unpublished observation). However, given such a variability, it would be necessary to confirm the present results by a cross-over randomly assigned trial.

In conclusion, our results confirm that some deficits in Alzheimer's disease are sensitive to cholinergic drugs and that further clinical trials with muscarinic agonists are worthwhile. They also

emphasise the usefulness of the reaction time paradigm as a tool for the psychopharmacological investigation of Alzheimer type dementia patients.

References

- 1 Coyle JT, Price DL, De Long MR. Alzheimer's disease: a disorder or cortical cholinergic innervation. *Science* 1983;219:1184-90.
- 2 Brinkman SD, Gershon S. Measurement of cholinergic drug effects on memory in Alzheimer's disease. *Neurobiol Aging* 1983;4:139-45.
- 3 Lamour Y, Dutar P, Jobert A. Excitatory effect of acetylcholine on different types of neurons in the first somatosensory neocortex of the rat: laminar distribution and pharmacological characteristics. *Neuroscience* 1982;7:1483-94.
- 4 Bird SJ, Aghajanian GK. The cholinergic pharmacology of hippocampal pyramidal cells: a microiontophoretic study. *Neuropharmacology* 1976;15:273-82.
- 5 Diagnostic and statistical manual of mental disorders (DSM III), 3rd ed, Washington: American Psychiatric Association, 1980:107-12.
- 6 Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol* 1975;32:632-37.
- 7 Kahn RL, Goldfarb AI, Pollack M, Peck A. Brief objective measures for the determination of mental status in the aged. *Am J Psychiatr* 1960;117:326-8.
- 8 Evarts EV, Teravainen H, Calne DB. Reaction time in Parkinson disease. *Brain* 1981;104:167-86.
- 9 Ferris S, Crook T, Sathananthan G, Gershon S. Reaction time as a diagnostic measure in senility. *J Am Geriatr Soc* 1976;24:529-33.
- 10 Harbaugh RE, Roberts DW, Coombs DW, Saunders RL, Reeder TM. Preliminary report: Intracranial cholinergic drug infusion in patients with Alzheimer's disease. *Neurosurgery* 1984;15:514-8.