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EFFECTS OF ACUTE INFUSION OF THE MUSCARINIC CHOLINERGIC AGONIST ARECOLINE ON VERBAL MEMORY AND VISUO-SPATIAL FUNCTION IN DEMENTIA OF THE ALZHEIMER TYPE

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Abstract

Raffaele, Kathleen C., Annamaria Berardi, P. Pearse Morris, Sanjay Asthana, James V. Haxby, Stanley I. Rapoport, and Timothy T. Soncrant: Effects of Acute Infusion of the Muscarinic Cholinergic Agonist Arecoline on Verbal Memory and Visuo-spatial Function in Dementia of the Alzheimer Type.
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1. Treatment of patients with dementia of the Alzheimer type (DAT) with arecoline, a muscarinic cholinergic receptor agonist, reportedly improves performance on a picture recognition memory task, but not on other memory measures. To examine further possible performance improvements following arecoline treatment, patients with DAT were treated with a 30 min intravenous infusion of arecoline (5 mg).
2. Psychometric testing was done at five time points (two before and three following the infusion). Patients were tested on a memory task (Buschke selective reminding) and a test of visuo-spatial performance (figure copying).
3. No net change from baseline was seen in mean scores following arecoline infusion. However, the changes in performance on the two tasks were correlated ($p<0.02$) over subjects at 10 min but not at 1.5 or 5.5 hr following the infusion.
4. This result suggests that although individual patients vary in their response to a given dose of arecoline, their responses are consistent across types of tasks. Thus the lack of a mean drug effect may be due to individual differences in response rather than to a lack of response.

Keywords: Alzheimer's disease, arecoline, brain, cholinergic function, memory.

Abbreviations: Alzheimer's disease (AD), dementia of the Alzheimer type (DAT).

Introduction

The central nervous system undergoes degenerative changes in individuals suffering from Alzheimer's disease (AD). In particular, markers of cholinergic nerve function (particularly the enzyme choline acetyltransferase) decrease during AD (Burchinsky, 1984; McGeer, 1984; DeKosky et al., 1985; Roth 1986). The demonstration of changes in other cholinergic markers (e.g. cholinergic receptors or acetylcholinesterase) with AD is controversial (Burchinsky, 1984; McGeer, 1984; DeKosky, 1985; Collerton, 1986).

Because of the apparent association between decreased cholinergic function and AD,

there have been many attempts to treat AD with pharmacologic cholinergic enhancement. Two methods have been attempted: 1) increasing the levels of acetylcholine in the brain by administering the precursors choline or lecithin (Wettstein, 1983; Becker and Giacobini, 1988) or by administering cholinesterase inhibitors such as physostigmine or tetrahydroaminoacridine (Christie et al., 1981; Brinkman and Gershon, 1983; Wettstein, 1983; Muramoto et al., 1984; Becker and Giacobini, 1988), and 2) directly stimulating cholinergic receptors with cholinergic agonists such as RS-86 or arecoline (Christie et al., 1981; Brinkman and Gershon, 1983; Bruno et al., 1986; Hollander et al., 1987; Mouradian et al., 1988; Tariot et al., 1988). In the only two studies of arecoline in dementia of the Alzheimer Type (DAT), acute infusions of drug were administered, and changes in performance were measured using picture recognition (Christie et al., 1981), or verbal memory, picture recognition, and serial naming (Tariot et al., 1988). Both studies found small improvements in picture recognition in DAT patients.

The current study, part of an ongoing investigation of the effects of arecoline on cognitive performance in patients with DAT, assessed performance on verbal memory and visuo-spatial construction tasks after administration of a single intravenous dose of arecoline to DAT patients.

Methods

Subjects

Subjects were 15 patients, ten men and five women, diagnosed with possible or probable Alzheimer's disease, according to NINCDS/ADRDA criteria (McKhann et al., 1984). Their ages ranged from 50 to 82 years (mean age 66.1 $\pm$ 10.3 (s.d.) years). All patients had mild to moderate dementia [Mini-Mental State Examination scores (Folstein et al., 1975) ranged from 17 to 28, mean 22.6 $\pm$ 3.1 (s.d.)]. All were screened for illness other than DAT and were medication-free. For all patients, consent to participate in this investigation was obtained both from the patient and from a concerned relative.

Drug Administration

Arecoline hydrobromide (Regis Chemical Co., Morton Grove, IL) 5 mg in normal saline (prepared as 100 ml sterile saline solution) was administered as a continuous intravenous infusion over 30 min. One hour prior to the start of the infusion, methscopolamine bromide (The Upjohn Co., Kalamazoo, MI) 2.5 mg was given orally. Methscopolamine, a muscarinic receptor antagonist that does not enter the brain, was administered to block peripheral autonomic actions of arecoline.

Cognitive Testing

Cognitive testing was conducted at five time points, two before and three after arecoline infusion. Pre-testing was conducted on the day before arecoline and on the

morning of the infusion (following methscopolamine administration). Post-testing was conducted at 10 min, 1.5 h, and 5.5 h following the end of the infusion.

Two cognitive tests were administered at each testing session: figure copying (Haxby et al., 1985) and Buschke selective reminding (Buschke, 1973). On figure copying, 3 to 5 figures were copied by the patient, using the same figures at each testing session. Figures were selected to have a difficulty level appropriate for each individual patient. For each figure, a patient's 5 attempts to copy it (one from each testing session) were ranked from 1 to 5 by three blinded raters, according to how closely it matched the template figure. On selective reminding, the patient attempted to learn a list of 8 words over 6 trials; after trial 1, the patient was reminded only of those words which were not recalled on the previous trial. Alternate forms of this test were used for each testing session. The selective reminding task was scored according to the number of words recalled by the patient: total recall represents the sum of the words correctly recalled by the patient in each of 6 trials (maximum score = 48).

Data Analysis

Analysis of Variance (one-way ANOVA with repeated measures) was used to determine whether there was a difference in performance within subjects across the time points following the infusion. Pearson's linear correlation coefficient was used to determine whether there was an association between change in performance on the two different tests, across subjects.

Table 1

Responses to Arecoline Infusion

Measure	Baseline	Mean Change from Baseline Score (Time after end of Arecoline infusion) 10 min	1.5 h	5.5 h
Selective Reminding (total recall, words recalled)	24.5 ± 8.7	-1.8 ± 5.1	-1.3 ± 7.1	-1.0 ± 3.4
Figure Copying (drawing rank)	3.1 ± 0.4	-0.4 ± 1.0	-0.2 ± 0.8	-0.1 ± 0.9

Mean ± S.D. for 11 patients. No significant change ($p>0.05$, ANOVA).
Range for selective reminding, 5-36.5; range for figure copying, 2.7-4.3.

Results

There was no difference between scores of the two pre-testing sessions; consequently, the average of these scores was used as baseline for comparison. Mean performance did

not differ across test sessions on either cognitive test (one-way ANOVA with repeated measures: Selective reminding, F=0.67, p=0.59; figure copying, F=1.53, p=0.22; see Table 1). A significant correlation was found, however, for changes in performance on the two tests at 10 min post infusion as compared to baseline (r=0.60, p<0.02, Fig. 1). Patients whose figure copying performance was improved at 10 min also had improved performance on the selective reminding task; patients whose figure copying performance had declined showed impaired performance on the selective reminding task. There was no significant correlation between changes in performance on the two tasks at 1.5 or 5.5 hours after arecoline (r=0.10 and r=0.20, respectively).

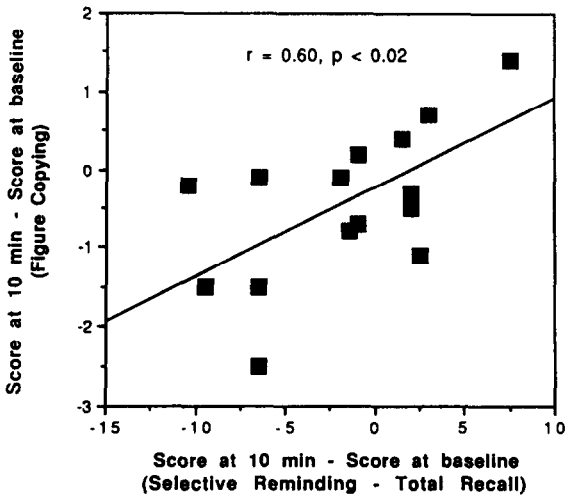

Fig 1. Correlation between changes in visuo-spatial construction (figure copying) and in verbal memory (selective reminding). Each point represents an individual patient.

Discussion

These results confirm marked individual variation in response to cholinergic drugs in DAT patients (Brinkman and Gershon, 1983; Mohs et al., 1985; Becker and Giacobini, 1988; Sherman et al., 1988). The correlation following drug infusion between performance for two different tasks, visuo-spatial construction and verbal memory, implies that the effect of drug administration, which varies among individuals, is not random. In addition, changes in performance on non-memory tasks following arecoline infusion show the importance of examining cognitive functions apart from memory when evaluating drug effectiveness in DAT patients.

The reason for the high degree of between subject variation in response to cholinergic

drugs is not apparent. Variance may reflect differences in pharmacokinetics (leading to different brain drug concentrations), or differences in intrinsic neuronal response. It may be important to evaluate each patient on a range of drug doses, in order to optimize the chance of finding a dose to which an individual subject will respond.

Conclusions

Individuals with dementia of the Alzheimer type vary in their response to cholinergic drug infusion. In spite of pronounced inter-subject variability, the direction of drug response (i.e. improvement or impairment) for an individual subject is consistent for different tasks. This consistency supports the conclusion that inter-subject variability in response to arecoline is not random, but is due to some characteristic of the individual subject.

References

BECKER, R.E. and GIACOBINI, E. (1988) Mechanisms of cholinesterase inhibition in senile dementia of the Alzheimer type. Drug. Devel. Res. 12: 163-195.

BRINKMAN, S.D. and GERSHON, S. (1983) Measurement of cholinergic drug effects on memory in Alzheimer's disease. Neurobiol. Aging 4: 139-145.

BRUNO, G., MOHR, E., GILLESPIE, M., FEDIO, P. and CHASE, T.N. (1986) Muscarinic agonist therapy of Alzheimer's disease. Arch. Neurol. 43:659-661.

BURCHINSKY, S.G. (1984) Neurotransmitter receptors in the central nervous system and aging: Pharmacological aspect. Exp. Gerontol. 19: 227-239.

BUSCHKE, H. (1973) Selective reminding for analysis of memory and learning. J. Verb. Learn. Verb. Behav. 12: 543-550.

CHRISTIE, J.E., SHERING, A., FERGUSON, J. and GLEN, A.I.M. (1981) Physostigmine and arecoline: effects of intravenous infusions in Alzheimer presenile dementia. Br. J. Psychiat. 138: 46-50.

COLLERTON, D. (1986) Cholinergic function and intellectual decline in Alzheimer's disease. Neurosci. 19: 1-28.

DEKOSKY, S.T., SCHEFF, S.W. and MARKESBERY, W.R. (1985) Laminar organization of cholinergic circuits in human frontal cortex in Alzheimer's disease and aging. Neurol. 35: 1425-1431.

FOLSTEIN, M.F., FOLSTEIN, S.E. and MCHUGH, P.R. (1975) "Mini-mental state": a practical method for grading the cognitive state of patients for the clinical. J. Psychiatr. Res. 12: 189-198.

HAXBY, J.V., DUARA, R., GRADY, C.L., CUTLER, N.R. and RAPOPORT, S.I. (1985) Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. J. Cerebral Blood Flow Metab. 5: 193-200.

HOLLANDER, E., DAVIDSON, M., MOHS, R.C., HORVATH, T.B., DAVIS, B.M., ZEMISHLANY, Z. and DAVIS, K.L. (1987): RS86 in the treatment of Alzheimer's disease: cognitive and biological effects. Biol. Psychiat. 22: 1067-1078.

MCGEER, P.L. (1984) Aging, Alzheimer's disease, and the cholinergic system. Can. J. Physiol. Pharmacol. 62: 741-754.

MCKHANN, G., DRACHMAN, D., FOLSTEIN, M., KATZMAN, R., PRICE, D. and STADLAN, E.M. (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under

the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurol. 34: 939-944.

MOHS, R.C., DAVIS, B.M., GREENWALD, B.S., MATHE, A.A., JOHNS, C.A., HORVATH, T.B. and DAVIS, K.L. (1985) Clinical studies of the cholinergic deficit in Alzheimer's disease II. Psychopharmacologic studies. J. Am. Geriat. Soc. 33: 749-757.

MOURADIAN, M.M., MOHR, E., WILLIAMS, J.A. and CHASE, T.N. (1988) No response to high-dose muscarinic agonist therapy in Alzheimer's disease. Neurol. 38: 606-608.

MURAMOTO, O., SUGISHITA, M. and ANDO, K. (1984) Cholinergic system and constructional praxis: a further study of physostigmine in Alzheimer's disease. J. Neurol. Neurosurg. Psychiat. 47: 485-491.

ROTH, M. (1986) The association of clinical and neurological findings and its bearing on the classification and aetiology of Alzheimer's disease. Br. Med. Bull. 42: 42-50.

SHERMAN, K.A., KUMAR, V., ASHFORD, J.W., MURPHY, J.W., ELBLE, R.J. and GIACOBINI, E. (1988) Effect of oral physostigmine in senile dementia patients: Utility of blood cholinesterase inhibition and neuroendocrine responses to define pharmacokinetics and pharmacodynamics. In: Central Nervous System Disorders of Aging: Clinical Intervention and Research, R. Strong, et al. (Eds)., pp 71-90, Raven Press, New York.

TARIOT, P.N., COHEN, R.M., WELKOWITZ, J.A., SUNDERLAND, T., NEWHOUSE, P.A., MURPHY, D.L. and WEINGARTNER, H. (1988) Multiple dose arecoline infusions in Alzheimer's disease. Arch. Gen. Psychiat. 45: 901-905.

WETTSTEIN, A. (1983) No effect from double-blind trial of physostigmine and lecithin in Alzheimer disease. Ann. Neurol. 13: 210-212.

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