SENSITIVITY OF THE COGTEST SYSTEM TO SCOPOLAMINE CHALLENGE: RELEVANCE TO STUDIES OF COGNITIVE ENHANCEMENT IN SCHIZOPHRENIA

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Summary

Object: In order to verify the sensitivity of the Cogtest system tests to pharmaceutical interventions, we administered a single 0.3mg subcutaneous dose of scopolamine to eight elderly healthy volunteers. Scopolamine has been routinely used to induce cognitive dysfunction in a bid to mimic the loss of acetylcholine transmission seen in patients with Alzheimer's disease.

Method: All participants were tested on a battery of three Cogtest assessments (www.cogtest.com), a word-learning task, a test of continuous performance, and one of strategic target detection. Participants were assessed 1-hour prior to drug administration and then 0:45, 1:45, 3:45 and 7:5 hours after drug.

Results: A marked decline in performance was seen 1.45 hours after drug administration. This was most noticeable (effect size, partial eta squared = 0.51) on the word learning task, with performance falling from a mean total trials score of 10.1 (SE 1.16) to 5.9 (SE 0.8) which is consistent with the known effects of scopolamine. Performance at 7.5 hours post drug administration was restored to baseline levels (9.9 ([SE 1.2]). Peak drug effects on a test of continuous performance showed a prolongation of latency for correct responses of 60msec, reducing to a 16msec prolongation 7.5 hours after dosing. As expected, performance on our test of strategic target detection was only mildly impaired by the administration of scopolamine.

Conclusions: The results of this study reaffirm our understanding of the dementia-mimetic properties of scopolamine. The study also confirms the capacity of the Cogtest battery to detect pharmacologically induced memory impairments in small groups of normal volunteers and paves the way for the use of Cogtest in cognitive disorders like schizophrenia and Alzheimer's disease.

Key Words: Cogtest – Scopolamine – Pharmaceutical interventions – Cognitive disorders

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Introduction

Recent regulatory guidelines from the Food and Drug Administration (FDA) and the European Medicines Evlauation Agency (EMEA) have further specified the use of cognitive testing as a means of measuring drug efficacy and safety (Harrison 2001, Wesnes & Harrison 2003). Traditionally assessments have been made using 'paper-and-pencil' assessments, but a wealth of data has suggested that computerized assessments improve the quality of psychometric data collection through increases in the reliability and validity of collected data (Wesnes & Harrison 2003). This increase in data quality has been recognized by opinion leaders in the field of cognitive testing to mark a major step forward.

A number of computerized systems have been developed as a means of aiding the use of cognitive testing in clinical trials. One such system is the Cogtest system (www.cogtest.com), which has been developed for use with a number of CNS indications in clinical trials and contains a variety of tests that are of utility in both psychiatric and neurological indications.

A number of the tests that comprise the Cogtest system are drawn from classes of task that have traditionally been shown to be sensitive to cognitive decline

in schizophrenia (Sharma et al. 2003, Hughes et al. 2003) as well as decline in dementia, and particularly probable dementia of the Alzheimer type (pDAT). A useful 'proof of principle' method of assessing test utility in such cognitive disorders is to employ the scopolamine model of dementia. Scopolamine is an alkaloid drug obtained from plants of the nightshade family (Solanaceae), chiefly from henbane, *Hyoscyamus niger.* Structurally similar to the neurotransmitter acetylcholine (AChE), scopolamine acts by interfering with the transmission of nerve impulses by acetylcholine in the parasympathetic nervous system and produces symptoms typical of parasympathetic system depression, i.e. dilated pupils, rapid heartbeat, and dry skin, mouth, and respiratory passages. Because scopolamine depresses the central nervous system, it is used as a sedative prior to anaesthesia and as an antispasmodic in certain disorders characterized by restlessness and agitation, e.g., delirium tremens, psychosis, mania, and Parkinsonism.

The utility of the scopolamine model is based on the observation that patients with schizophrenia and pDAT suffer decreased AChE transmission as a result of the pathology characteristic of the diseases **.** Thus by reversibly blocking AChE transmission it is possible to mimic the memory deficits observed in schizophrenia and pDAT. This has been demonstrated a number of times since Drachman & Leavitt reported their findings in 1974 (e.g. Kopelman & Corn 1988, Wesnes et al. 1991). A review of the pertinent literature suggests that word list learning and vigilance (to some extent) tasks with delayed recall are particularly sensitive to the disruptive effects of scopolamine (e.g. Brass et al. 1995). A single acute administration of scopolamine in healthy study participants has been also shown to impair visuospatial praxis and psychomotor speed (Drachman & Leavitt 1974, Drachman 1982, Flicker et al. 1992).

Some classes of cognitive task appear to be relatively immune to the deleterious effects of scopolamine. Examination of the literature suggests that abstract rule learning tasks, such as the Intra-Extra-Dimensional (IED) shift task and the Wisconsin Card Sorting Test (WCST), are affected in diseases in which pathological changes have occurred in brain regions within, or targeting, prefrontal cortical structures, but to a lesser degree in temporal lobe areas. For example, Robbins et al. (1994) have shown that patients with Parkinson's disease, Multiple Systems Atrophy and Progressive Supranuclear Palsy are all impaired on the IED task. By contrast even temporal lobe removal and amygdalohippocampectomy appear to leave IED performance relatively uninjured (Owen et al. 1991). The expected performance of patients with pDAT is somewhat mixed. Sahakian et al. (1990) have shown that the performance of a significant proportion of patients with mild pDAT is indistinguishable from that of controls. However, more clinically impaired patients experienced problems with this task. On balance the authors claim 'sparing of attentional shifting in patients early in the course of DAT'.

In this study we employed a word list learning task and a continuous performance task from the Cogtest battery, both of which we expected to be negatively effected by the administration of scopolamine. We also used a strategic detection task from the same battery that has some similarities with the IED and WCST. We hypothesized that performance on this task would be relatively unaffected by the administration of scopolamine.

Design

This trial was a repeated measures design study in which eight study participants received a single, subcutaneous dose of 0.3mg of scopolamine. The total study duration was one day and the trial was undertaken in two centres in the UK. Pre-drug administration performance (t –1 hour) was to be compared with post drug performance 45 minutes, 1 hour 45 minutes, 3 hours 45 minutes and 7 hours 30 minutes after drug administration.

Previous research (Ebert et al. 1998) has reported that maximum serum concentrations of scopolamine occur 10 to 30 minutes after drug administration and that elimination half-life is approximately 220 minutes. Based on these data we expected to see peak drug effects either 45 minutes or 1 hour 45 minutes after drug administration. Assessments were also scheduled 3 hours 45 minutes after drug and then finally 7 hours 30 minutes post drug administration. Given the known pharmacodynamic characteristics of a 0.3mg dose of scopolamine, we expected baseline cognitive function to be restored by the time the final assessment was carried out.

Our cognitive primary efficacy variables were three tasks from the Cogtest battery of cognitive tests

Word List Memory (WLM) - This is an auditory-verbal recall test adopting the widely used selective-reminding paradigm. Study participants have to recall as many as possible of 16 words that have been auditorily presented by the computer. This method of administration enables standardization of quality and speed of presentation. On the second trial, the computer repeats only those words that the study participant has not recalled and the study participant is then asked to try to recall all 16 words again. Following each presentation the examiner records the study participants' responses on a specially constructed screen, enabling immediate and automatic scoring. This process is repeated up to 5 times in total.

Continuous Performance Task (CPT) - This is an experiment of conditional target-non-target discrimination ability, sustained attention, and the ability to sustain effort in a cognitively demanding situation. In this test, the study participant is instructed to respond with a right mouse press when an 'X' is preceded by an A. The left mouse button is pressed for all other stimuli, including an A, an X that was not preceded by an A, and any other letter. Stimuli are selected according to the structure and randomization algorithm set out in this document. Twenty percent of the stimuli are targets (A-X). Stimuli are presented for 200msec each. The inter-trial interval varies across trials and may be 1.5, 2.0 or 2.5 seconds (this includes the duration of the stimulus), so the average ITI is 2.0 seconds. This is randomized across 150 trials. Practice trials are given and the study participant is trained in the correct performance of the

test before formal testing is initiated. The outcome measure selected for analysis in this study was latency for correct responses.

Strategic Target Detection (STD) - This test is similar to the paper-and-pencil 'cancellation' tests or the 'cross-out' subtest of the WAIS-III, where study participants are required to cross out target stimuli embedded among distracters. In this computerized version, the study participant touches the target stimuli (shapes) directly on the touch screen. An added feature of this test is that the study participant is not told in advance which of the stimuli is the 'target'. Instead, they must learn which is the correct target by choosing one of the stimuli and observing feedback that indicates whether the choice was right or wrong. This feature is similar to that used in the WCST, where the correct 'rule' is learned by study participants only from examiner feedback. Another feature of this test similar to the WCST is that the target stimulus changes after a criterion number of consecutive correct responses. Thus study participants must: (1) select stimuli until they learn which is the correct (reinforced) target stimulus; (2) select the target stimuli as rapidly as possible until achieving the criterion number of them, at which point the target stimulus changes; (3) stop selecting the previously reinforced stimulus, and learn which is the new target stimulus; (4) continue through these cycles until the end of the test. The selected outcome measure for this task was mean correct response latency.

Participants

Eight female participants were recruited for the study. Inclusion in the study required that obtained signed and dated ethics committee approved, written Informed consent and Assent from the volunteer in accordance with local regulations. Participants were to be age between 40 to 75 years, inclusive and to be fluent in local language. Finally, in the opinion of the Investigator, the volunteer had to have been compliant and have a high probability of completing the study.

Any one of the following excluded a volunteer from this study; Significant neurological disease that may affect cognition; current presence of a clinically significant major psychiatric disorder, according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), that could affect the volunteer's ability to complete the study; current clinically significant systemic illness or symptoms (e.g., hallucinations, cardiovascular disease) that may deteriorate or affect the volunteer's safety or ability to cooperate with testing during the study; any clinically relevant abnormality in routine haematology or biochemistry; known hypersensitivity to scopolamine or related compounds; any condition where a dose of scopolamine would be contraindicated e.g. known prostatic hypertrophy, significant bradycardia (heart rate of 50 or less/min) and history of family history of closed angle (congestive) glaucoma; history of clinically evident stroke or clinically significant carotid or vertebrobasilar stenosis or plaque; a clinically significant infection within the last 30 days (e.g., chronic persistent or acute infection); myocardial infarction within the last 2 years; history of clinically significant cancer within the last 5 years; other clinically significant abnormality on physical, neurological, or laboratory examination or on electrocardiogram (ECG) that, in the opinion of the Investigator, precluded the volunteer from the study; excessive smoking (more than 15 cigarettes per day); history of alcohol or drug dependence within the last 2 years; current use of anticonvulsant, anti-Parkinson's, anticoagulant or narcotic medications; medications with the potential to effect cognition (including but not limited to anxiolytics, sedatives, hypnotics, antipsychotics, antidepressants, OTC sleeping aids, anti-allergy medications, or thyroid and B12 supplements) are excluded unless maintained on a stable dosing regimen for at least 3 months prior to Day 0; volunteers who have used antibiotics for the treatment of a clinical infection within 30 days of the study day; volunteers treated with immunosuppressive medications (e.g., corticosteroids) within the last 90 days or chemotherapeutic agents within the last 3 years.

Our final criterion for exclusion was the presence of any clinically significant, concomitant disease that in the opinion of the investigator could interfere with the study participant's inclusion in the study or confound the outcome variables. The trial was performed in accordance with the Declaration of Helsinki and its subsequent revisions. This study was approved by the appropriate local ethics committees.

Results

All participants were white females with an average age of 69.1 years. Precise ages and years of education for each study participant are shown in Table 1.

Consistent with the known effects of scopolamine, a decline in performance was seen on the word memory task, with performance falling from a mean total trials score of 10.1 (SE 1.16) to 5.9 (SE 0.8). Also consistent with our knowledge of scopolamine's effects, performance at 7.5 hours was restored to baseline levels (9.9 [SE 1.2]). This effect was found to be statistically significant when analysed by repeated measures analysis of variance (F=3.75,df 1,7, P=0.01; partial eta squared = 0.349). Performance at 1.45hrs (t=2.773, d.f=7, p=0.028) and at 3.45hrs (t=2.739, d.f. =7, p=0.029) was significantly worse than the baseline pre-drug administration performance (quad F = 7.249, d.f =1,7, p=0.031,

Table 1. *Baseline characteristics of study participants*

Study participant	Age (in years)	Years of education
One	72	12
Two	69	11
Three	75	16
Four	75	13
Five	62	13
Six	63	13
Seven	71	16
Eight	66	16

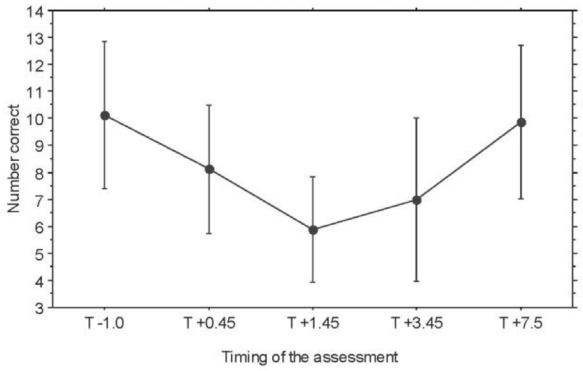

Figure 1. *Performance on Word List Memory task. Error bars represent 95% confidence intervals*

partial eta squared 0.51) as shown in Figure 1

Analysis of latency for correct responses on the CPT task showed a modest increase in latency of 59msec from predrug assessment (588msec, SD=148) to peak drug activity (648msec, SD=109). However, this effect was not significant (F=1.262, p=0.3123). Latency returned to values close to predrug levels 7.5 hours after administration (604msec, SD=135).

Finally, whilst modest elevations of latency were seen on the STD task at the t +0.45 and t +1.45, these effects were slight and were not found to be statistically significant (F<1).

Discussion

The results of our study have reaffirmed the cholinergic blockade effects of scopolamine upon cognitive function. Performance on the WLM declined by half at peak drug effects and later returned to baseline levels (see Figure 1). Performance on our CPT was also impaired though did not reach significance. As expected, performance on our third task, STD, showed little or no evidence of drug effect.

Whilst unsurprising in the context of what is known of scopolamine's effects upon cognitive function, our findings are important and useful validation of the selected tasks from the Cogtest system. Of particular interest and potential utility is the robust effect of scopolamine upon word list learning. As a class of test, verbal memory tasks have been shown to demonstrate utility in studies of patients with dementia and especially pDAT. Such tests have also been proposed as good candidates for use with individuals believed to have incipient dementia, a staging commonly characterized as Mild Cognitive Impairment (MCI). Recent reviews of MCI by Petersen et al. (2001) have suggested that endpoints in clinical trials of drugs for dementia 'will likely be limited to sensitive tests of delayed memory (verbal and visual) and clinician's global ratings'. Some evidence in support of this proposition has been provided by Grundman et al. (2004). Their study of controls, patients with pDAT and MCI has shown that amongst the cognitive subtests of the Alzheimer's Disease Assessment Scale (ADAS-cog, Rosen et al. 1984) it was the tests of verbal recall and recognition that best discriminated between the different patient groups.

A major deficiency of the ADAS-cog is the absence of tests designed to evaluate attention, a cognitive faculty known to be compromised in the very earliest stages of dementia (e.g. McKeith et al. 2000). Some attempts have been made to remedy this deficiency though the inclusion of 'paper-and-pencil' tests and even clinical ratings of concentration and distractibility. However, these measures are unlikely to be capable of accurately assessing these important cognitive skills. In contrast, commentators have pointed out that the inclusion of accurate measures of response latency have the capacity to augment our characterization of cognitive dysfunction in dementia (Cummings 2000). The inclusion of computerized latency measures such as the Cogtest CPT provides developers with an excellent opportunity to more accurately and comprehensively assess the effects of their drug.

Finally, a number of commentators have suggested that well-assembled batteries of cognitive tests have the potential not just to measure change in dementia drug trials, but also to assist with the selection and diagnosis of study participants. For example, Petersen et al. (2001) propose that 'A brief battery, including measures of new learning, delayed recall, attention and executive function, could provide valuable information for screening and diagnosis if interpreted properly'. We believe this approach has significant merit. Combinations of reliable, valid and sensitive cognitive assessments have significant potential as a means of improving methods of patient selection and the measurement of drug safety and efficacy.

In the field of schizophrenia the MATRICS project (www.matrics.ucla.edu) has increased the pace of drug development and clinical trails of cognitive enhancement in schizophrenia, in such trails studies with batteries that have been tried in schizophrenia and are available in multiple languages will be of benefit.

References

Brass EP, Polinsky R, Sramek JJ, Moore M, Jones D, Veroff AE, Wardle TS, Cutler NR (1995). Effects of the cholinomimetic SDZ ENS-163 on scopolamine-induced cognitive impairment in humans. *J Clin Psychopharmacol* 15, 58-62.

Cummings JL (2000). Cholinesterase inhibitors: expanding applications. *Lancet* 356, 9247, 2024-5.

Drachman DA (1982). Aging and dementia: insights from the study of anticholinergic drugs. In, Katzmann R (ed) *Biological aspects of Alzheimer's disease*, Benbury Report 15, 363-9.

Drachman DA, Leavitt J (1974). Human memory and the cholinergic system: a relationship to aging? *Arch Neurol* 30,113-21.

Ebert U, Siepmann M, Oertel R, Wesnes KA, Kirch W (1998). Pharmacokinetics and pharmacodynamics of scopolamine after subcutaneous administration. *J Clin Pharmacol* 38, 8, 720-6.

Flicker C, Ferris SH, Serby M (1992). Hypersensitivity to scopolamine in the elderly. *Psychopharmacology* 107, 437-41.

Grundman M, and the Alzheimer's Disease Cooperative Study (2004). Mild Cognitive Impairment can be distinguished from Alzheimer's disease and normal aging for clinical trials. *Arch Neurol* 61, 59-66.

Harrison J (2001). Cognitive testing and drug development. *Clinical Research Focus* 12, 5-11.

Harrison J (2002). Routine cognitive testing for all drugs? *Drug Disc Today* 7, 101-102.

Hughes C, Kumari V, Soni W, Das M, Binneman B, Drozd S, O'Neil S, Mathew V, Sharma T (2003) Longitudinal study of symptoms and cognitive function in chronic schizophrenia. *Schizophr Res* 59, 2-3,137-46.

McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R (2000). Efficacy of rivastigmine in dementia with Lewy bodies: a randomised, double-blind, placebo-controlled international study. *Lancet* 356, 9247, 2031-6.

Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW (1991). Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions or amygdalo-hippocampectomy in man. *Neuropsychologia* 29, 10, 993-1006.

Petersen RC, Stevens JC, Ganguli M, Tangalos E, Cummings J, DeKosky ST (2001). Practice parameter: Early detection of dementia: Mild Cognitive Impairment (an evidence based review). *Neurology* 56, 1133-1142.

Robbins TW, James M, Owen AM, Lange KW, Lees AJ, Leigh PN, Marsden CD, Quinn NP, Summers BA (1994). Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *J Neurol Neurosurg Psychiatry* 57, 1, 79-88.

Robbins T, Semple J, Kumar R, Truman M, Shorter J, Ferraro A, Fox B, McKay G, Matthews K (1997). Effects of scopolamine on delayed-matching-to-sample and paired associates tests of visual memory and learning in human subjects: comparison with diazepam and implications for dementia. *Psychopharmacology* 134, 95-106.

Rosen WG, Mohs RC, Davis KL (1984). A new rating scale for Alzheimer's disease. *Am J Psychiatry* 141, 11, 1356-64.

Sahakian BJ, Downes JJ, Eagger S, Evenden JL, Levy R, Philpot MP, Roberts AC, Robbins TW (1990). Sparing of attentional relative to mnemonic function in a subgroup of patients with dementia of the Alzheimer type. *Neuropsychologia* 28, 11, 1197-213.

Sharma T, Hughes C, Soni W, Kumari V (2003). Cognitive effects of olanzapine and clozapine treatment in chronic schizophrenia. *Psychopharmacology* 169, 3-4, 398-403.

Wesnes K, Harrison J (2003). The evaluation of cognitive function in the dementias: methodological and regulatory considerations. *Dial Clin Neurosci* 5, 77-88.