THE EFFECTS OF SCOPOLAMINE IN ELDERLY VOLUNTEERS USING THE COGTEST BATTERY

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ABSTRACT

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 N=8 elderly study participants. 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. All participants were tested on a battery of three Cogtest assessments: a test of continuous performance, one of strategic target detection and a word-learning task. Participants were assessed 1-hour prior to drug administration and then 0:45, 1:45, 3:45 and 7:5 hours after drug. Consistent with the known effects of scopolamine, a marked decline in performance was seen 1.45 hours after drug administration. Also consistent with known effects, cognitive decline was most marked 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). Performance at 7.5 hours post drug administration was restored to baseline levels (9.9 ([SE 1.2]). This effect was found to be statistically significant when analysed by ANOVA (F=3.75, P=0.01). 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. Consistent with our hypotheses, performance on our test of strategic target detection was only mildly impaired by the administration of scopolamine. 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 the detect scopolamine induced memory impairments in small groups of normal volunteers.

INTRODUCTION

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, which has already found utility in a number of clinical drug trials (Bilder et al., 2003). The system has been developed for use with a number of CNS indications and contains a variety of tests likely to be 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 decline in dementia, and particularly probable dementia of the Alzheimer type (pDAT). A useful 'proof of principle' method of assessing test utility in pDAT 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. 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.

In this study we employed a word list learning task and a continuous performance task, both of which we expected to be negatively effected by the administration of scopolamine. We also selected a strategic detection task 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.

METHODS

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

Figure 1: Screenshot Examples of Cogtest battery tests

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. 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 computerised version, the study participant touches the target stimuli (shapes) directly on the touch screen.

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 standardisation 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.

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 aged between 40-75 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.

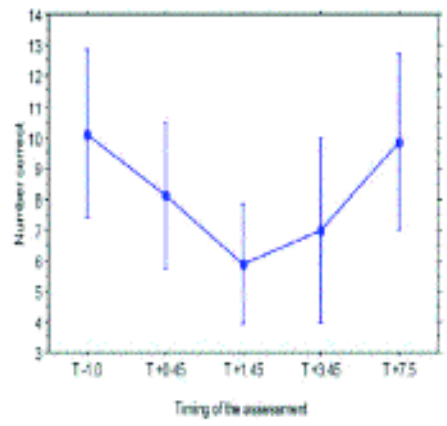
RESULTS

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.

Table1. Descriptive Statistics for Computerised Tests at Baseline

Study participant	Age (in years)	Years of education
One	72	12
Two	69	11
Three	75	18
Four	75	13
Five	62	13
Six	63	13
Seven	71	16
Eight	68	18

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 ANOVA (F=3.75, P=0.01) and is shown in Fig. 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 Fig. 1). Performance on our CPT was also impaired though this did not reach significance. As expected, performance on our third task, STD, showed little or no evidence of drug effect.

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 has the capacity to augment our characterisation 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.

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