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ASSESSMENT OF NEUROLOGICAL EFFECTS OF DRUGS ON OCULOMOTOR AND VISUAL FUNCTION IN THE PRIMATE

Annual Report

E. Gregory Keating, Ph.D.

December 15, 1983

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

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Research Foundation of S.U.N.Y.
Upstate Medical Center
750 East Adams Street
Syracuse, New York 13210

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The eye movements of cynomolgous monkeys (Macaca fascicularis) were recorded with the magnetic search coil technique while they searched for camouflaged targets or tracked moving targets. A preliminary analysis was completed of the effects of atropine on performance of the Visual Search and Target Tracking test as well as on the effects on the Visual Search test of atropine/pralidoxime and pyridostigmine. Atropine at all levels tested (0.014 – 0.25 mg/K) caused mydriasis and some drift in eye fixations. Performance on visual search and tracking of targets was consistently disrupted only at the highest dose. The decrements in search were not drastic but atropine more substantially interfered with the gain, phase and continuity of tracking eye movements.

Atropine/pralidoxime (0.014/1.0 – 0.25/8.0 mg/K) caused mydriasis, excessive eye blinks, some drift in fixations but had little effect on performance of visual search.

Pyridostigmine (14 mg/K daily for 2 weeks, orally) had no detectable effect on the monkey's neurological status or its performance of visual search.
Summary

A number of cholinergic agents are deemed useful as prophylactics or antidotes to organophosphate poisoning yet have their own toxic effects. Dosages of these agents which are known to not grossly disrupt behavior may nonetheless degrade performance of sophisticated tasks required of the personnel of a modern mechanized army.

The contract uses an animal model (primate) to assess the effects of cholinergic drugs on the performance of visual search and tracking tasks which mimic skills generally used in the field.

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Foreword

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (DHEW Publication No. (NIH) 78-23, Revised 1978.

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Methods of Research

The following annual progress report is submitted in compliance with the terms of our contract "Assessment of Neurological Effects of Drugs on Oculo-motor and Visual Function in the Primate." The report covers data collected during the second year of the contract from August, 1982, through September, 1983.

The purpose of the contract is to develop an animal model (primate) for visual search and target tracking performance so as to assess the behavioral effects of cholinergic drugs (e.g., atropine, 2-PAM Cl, physostigmine, pyridostigmine). Two tasks have been developed to mimic the visual search and tracking skills required of military personnel in the field. A search task requires the monkey to find and fixate a target spot embedded in a field of distractors. A second tracking task requires the monkey to track and predict the trajectory of a moving target. We use the magnetic search coil technique to record their eye movements during the tasks. The data provide indices of basic visual and oculomotor competence as well as measures of more cerebral or attentional decrements caused by cholinergic agents.

During the past year, drug trials with the visual search test continued with cynomolgus monkeys (Macaca fascicularis). The schedule of drug trials completed up the end of the report period is shown in Table 1.

Table 1

| Subject 1 | B D C C C B D D A E E A* A |
| Subject 2 | U C C E E B D A B* A B |
| Subject 3 | A* A D B D B C E C E F F |
| Subject 4 | C* A D B C A E B E D F F |
Physostigmine (A = .025; B = .050; C = .075 mg/K)
Subject 1  D A B B A D C C
Subject 2  B D B C D A C A
Subject 3  D C B A A D C B* B
Subject 5  D D C C* A A B B

Atropine (A = .014; B = .045; C = .14; D = Saline; E = .25 mg/K)
Subject 1  D C A E D E C B B A
Subject 2  C C B A E B E A D D
Subject 3  E A C D A C B E B B
Subject 6  D D C A E A B E B C

Atropine-Pralidoxime (combination of doses shown above for individual drugs)
Subject 1  A D E A B C E B C D
Subject 2  D B E C B D A E A C
Subject 3  D D C A E A* B E B C

Pyridostigmine (7 mg/K twice daily for 14 days)
Subject 1  Completed trial
Subject 2  Completed trial
Subject 3  Completed trial

TARGET TRACKING TEST

Atropine (A = .014; B = .045; C = .14; D = Saline; E = .25 mg/K)
Subject 1  C E A E A B C D B
Subject 2  E C B A A C D B
Subject 3  A B
Subject 6  D E C C A B

*Technical imperfections invalidate data.
Results on the effects of pralidoxime and physostigmine on Visual Search have been presented previously (cf. first annual report). The present report provides a preliminary analysis of the effects of atropine on both the Visual Search and the Target Tracking test and the results on the Visual Search test from the atropine-pralidoxime and pyridostigmine trials. The report includes for each of these drugs a summary of any observed neurological effects, description of oculomotor changes as characterized by unanalyzed strip-chart recordings of the eye movement traces, and finally, graphs of performance on the Visual Search and Tracking tests. Performance on these tests is expressed as "Z scores" in which the monkeys' behavior under the influence of the drug is normalized to the mean and variation of its baseline behavior. Specifically, \[ Z = \frac{X_D - M_B}{\sigma_B} \]

\( X_D \) = average performance over the trials of Visual Search or Target Tracking on the day of the drug

\( M_B \) = mean performance over all blocks of trials on the baseline days (20-30 days of testing)

\( \sigma_B \) = standard deviation of the baseline blocks

Data were collected during an Early (15-25 minutes; Atropine = 45-65 minutes) and a Late (40-50 minutes; Atropine = 65-85 minutes) session after drug administration. Under the assumption that the "Z scores" distribute normally, performance within \( Z < \pm 1.96 \) is considered to represent the limits of normal behavior. In practice, our previous experience with this measure and the Visual Search test is that reliable drug decrements are signalled by Z scores falling well outside their limits.

Visual Search: Graphs show the results for 3 measures: percent of trials on which the monkey successfully fixated the target and, on successful trials, the time and the number of fixations needed to find (fixate) the target.

Target Tracking: The graphs plot over time the positions of the target and the monkey's gaze. Targets moved horizontally and we collected only the horizontal eye movement made in response. A good informal idea of tracking performance can be gleaned from examining by eye the degree of fit between eye and target position traces. We've developed three measures to characterize performance more formally. Target and eye position signals were sampled every 3 msec., digitized, then differentiated into velocity traces. Failure to track a target with smooth pursuit movements forces the monkey to catch up to it with saccadic eye movements. A velocity criterion was used to detect saccades and arrive at the first measure: percent of time spent in saccades rather than smooth pursuit movements. To examine the dynamics of just the pursuit epochs the saccades were then removed from the record and a cross-correlation analysis of the "cleaned" eye velocity trace was carried out, in general outline according to the method described by Cassell (Med. Biol. Eng., 1973, p. 755). The target velocity trace was first correlated with itself and the first positive peak of the autocorrelation function was taken as a measure of target velocity (\( V_T \)). The autocorrelated target trace was cross-correlated
with the monkey's "cleaned" velocity trace. The first positive peak of the cross-correlation was considered an index of the monkey's best tracking performance ($V_E$) and expressed as a second measure:

$$\text{Gain} = V_E / V_T$$

The third index was a measure of phase or the average tendency of the monkey to lead or lag behind the target:

$$\text{Phase (in msec)} = T_{VE} - T_{VT}$$

$T_{VE}$ is the time of occurrence of the monkey's best performance relative to a target time ($T_{VT} = 0$).

During each session monkeys were tested under four target conditions. The target could travel at one of two velocities and through either a predictable or unpredictable trajectory. The Predictable condition was a regular sinusoidal function of 9° amplitude. With such a function, the subject can predict that whenever the target slows to zero velocity it will reverse direction. The Unpredictable condition was a "random walk" of sinusoids. Each time the target sinusoid crossed zero velocity, a random number table was consulted to see if the next half-cycle of the target function would reverse direction and complete the sinusoidal cycle or instead continue on with a sinusoidal velocity in the same direction. This left the monkey uncertain of the exact trajectory and less able to generate a predetermined ballistic program of movement to it. The two conditions were run at either 0.4 or a faster 1.4 Hz.

Only results from the two conditions using the faster velocity target are reported here. As with Visual Search, the formal measure on pursuit collected during drug trials were converted to Z scores of performance relative to baseline scores. However, the plots of eye trajectories provide some absolute gain, phase, and percent-of-saccades scores achieved during some drug trials to give some feeling for typical actual scores achieved under these testing conditions.

Atropine Summary

.014 mg/K

Slight pupillar mydriasis appeared; the monkeys were otherwise neurologically normal. Eye records were for the most part normal, but with excessive eye blinks and the suggestion of slight drift of fixations in 2 subjects.


Target Tracking: Normal.
.045 mg/K

Moderate mydriasis and continual lip movements indicative of a dry mouth occurred in all subjects, but with no other symptoms of muscle weakness. Oculomotor record was mostly normal but contained excessive eye blinks and the hint of shorter and perhaps slightly drifting fixations.

Visual Search: Normal.

Target Tracking: Normal.

.14 mg/K

Mydriasis and dry mouth was variable and ranged from moderate to severe. Slight ptosis occurred in one monkey, but limb movement and posture did not indicate general muscle weakness. The oculomotor record at this dose displayed obvious drift in fixations and the saccadic traces were sloped (slowed). Fixations were shorter than normal -- interrupted more frequently by small shifts of gaze. There was slight dysmetria which included both over- and undershooting of the target.

Visual Search: Largely normal, but with some variability between subjects and between first and second testing of this dose. Two subjects (1,2) required slightly more fixations to find the target on the first but not the second testing. This dose did not appear to disrupt the monkey's willingness to search for targets.

Target Tracking: Results were similar to those on the Visual Search test. In general the gain and phase of pursuit were normal but with exceptions. Subject 1's tracking was abnormal in one session, that of Subject 2's faulty in both sessions of this dose.

.25 mg/K

Mydriasis was quite pronounced although the pupils were not dilated to their limits. Dry mouth and ptosis were seen but no obvious skeletal weakness. The oculomotor record was markedly disfigured by eye blinks, drifting and fractured fixations.

Visual Search: Testing of two subjects proceeded smoothly. The other two appeared less motivated and paused occasionally between trials. The effect on performance is reflected in fewer targets acquired and an increase in time and number of fixations to find the target. However, these changes did not show up consistently and at their worst were not drastic decrements.

Target Tracking: Decrements in formal measures of this task were clearer and more consistent than on the Visual Search test and were reflected in lowered gains, a greater phase lag behind the target, and an increase in the amount of time spent making corrective saccades to catch up to the target.
ATROPINE

EYE MOVEMENTS DURING SEARCH

Figure 1
ATROPINE
PERCENT OF TARGETS FIXATED

SUBJECT 3

SUBJECT 6

Figure 3
ATROPINE
TIME TO FIND TARGET

SUBJECT 1

SUBJECT 2

Z SCORE

Z SCORE

SAL .014 .045 .14 .25 MG/K
ATROPINE
TIME TO FIND TARGET

SUBJECT 3

Z SCORE

SUBJECT 6

Z SCORE

MG/K

Figure 5
ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

SUBJECT 1

Z SCORE

SUBJECT 2

Z SCORE

MG/K

figure 6
ATROPINE
NUMBER OF FIXATIONS TO FIND TARGET

\[ Z \text{ SCORE} \]

\[ \text{SAL} \quad 0.014 \quad 0.045 \quad 0.14 \quad 0.25 \]

\[ \text{MG/K} \]

\( \triangle \quad \text{EARLY} \)
\( \circ \quad \text{LATE} \)

SUBJECT 3

SUBJECT 6
Atropine "Worst Case" Block Scores on Visual Search
Subject 1; .25 mg/K; Early

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<td>97.3</td>
<td>2.6</td>
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<td>Time to find target (msec.)</td>
<td>298</td>
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<td>Number of fixations to find target</td>
<td>1.16</td>
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<td>Saccadic velocity (deg./sec.)</td>
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<td>Fixation drift (degrees)</td>
<td>.34</td>
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<td>Fixation duration (msec.)</td>
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<td>55</td>
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<td>Error in fixating target (deg.)</td>
<td>.37</td>
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<td>.51</td>
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ATROPINE - EYE MOVEMENTS DURING TARGET TRACKING

TARGET POSITION

EYE POSITION

SLOW (9° AMP, 0.4 Hz) PREDICTABLE TARGET

SLOW UNPREDICTABLE TARGET

FAST (9° AMP, 1.4 Hz) PREDICTABLE TARGET

FAST UNPREDICTABLE TARGET

G PH SAC.
0.97 0.00 0.50

0.90 27.0 1.32

0.85 9.00 7.50

0.62 54.0 5.01

MG/K 0.014
ATROPINE: TRACKING - FAST PRED.

GAIN

SUBJECT 1

Z SCORE

SUBJECT 2

Z SCORE

Mg/K

FIGURE 12
ATROPINE: TRACKING - FAST PRED.
GAIN

SUBJECT 6

Z SCORE

SAL 0.014 0.045 0.14 0.25 + - TO BE COLLECTED

MG/K

Figure 13
ATROPINE: TRACKING - FAST PRED. PHASE

SUBJECT 1

SUBJECT 2

MG/K

Figure 14
ATROPINE: TRACKING - FAST PRED. PHASE

SUBJECT 6

Z SCORE

SAL 0.014 0.045 0.14 0.25

+ - TO BE COLLECTED

MG/K

figure 15
ATROPINE: TRACKING - FAST PRED.
PERCENT OF TIME IN SACCades

\[ \Delta \quad \text{EARLY} \]
\[ \bigcirc \quad \text{LATE} \]

**SUBJECT 1**

**SUBJECT 2**

```
  SAL  .014  .045  .14  .25
  MG/K
```

*figure 14*
ATROPINE: TRACKING - FAST PRED.
PERCENT OF TIME IN SACCADIES

EARLY
LATE

SUBJECT 6

MG/K
figure 17
Atropine - Pralidoxime Summary

**0.014 mg/K atropine + 1.0 mg/K pralidoxime**

- Neurological status was normal but for the hint of mydriasis. The oculomotor record was also normal.
- Visual Search: Normal.
- Target Tracking has not yet been tested.

**0.045 + 2.0 mg/K**

- Slight to moderate mydriasis but not other neurological symptoms appeared. The oculomotor record revealed shorter fixations, and sloping saccades in both early and late sessions. These abnormalities were subtle in appearance but the differences from normal were supported by shorter average durations of fixations and slowed saccadic velocities.
- Visual Search: Consistently normal performance.

**0.14 + 4.0 mg/K**

- Neurological and oculomotor status were much the same as the previous lower dose. The mydriasis was obvious but not severe. Fixations were often interrupted by small shifts of gaze and eye blinks but the monkeys were able to hold a point without much drift.
- Visual Search: Consistently normal.

**0.25 + 8.0 mg/K**

- Mydriasis and, in two animals, ptosis were the only neurological symptoms. The oculomotor records were not dramatically worse than at lower doses.
- Visual Search: Normal except for performance during one late session with one subject (1). The "worst case" block scores for this session are shown on the following table.
ATROPINE/PAM
EYE MOVEMENTS DURING SEARCH

NORMAL

HORIZONTAL

VERTICAL

VERTICAL

0.014/1.0 MG/K

HORIZONTAL

Figure 18
ATR-PAM
PERCENT OF TARGETS FIXATED

EARLY
LATE

SUBJECT 3

Z SCORE

SAL .014 .045 .14 .25
+ - TO BE COLLECTED

MG/K
ATR-PAM
TIME TO FIND TARGET

EARLY

LATE

SUBJECT 3

Z SCORE

SAL .014 .045 .14 .25

+ - TO BE COLLECTED

MG/K

figure 22
ATR-PAM
NUMBER OF FIXATIONS TO FIND TARGET

---
&
---
EARLY
LATE

SUBJECT 1

Z SCORE

SUBJECT 2

Z SCORE

SAL 0.014 0.045 0.14 0.25
Mg/K

Figure 23
ATR-PAM
NUMBER OF FIXATIONS TO FIND TARGET

---

EACH

SUBJECT 3

---

Z SCORE

---

SAL .014 .045 .14 .25
+
- TO BE COLLECTED

---

MG/K

figure 29
Atropine - Pralidoxime "Worst Case" Block Scores on Visual Search
Subject 1; .25 + 8.0 mg/K; Late Session

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<tr>
<td>On successful trials:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to find target (msec.)</td>
<td>308</td>
<td>13</td>
<td>365</td>
</tr>
<tr>
<td>Number of fixations to find target</td>
<td>1.22</td>
<td>0.07</td>
<td>1.50</td>
</tr>
<tr>
<td>Oculomotor:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saccadic velocity (deg./sec.)</td>
<td>282</td>
<td>5.1</td>
<td>275</td>
</tr>
<tr>
<td>Fixation drift (degrees)</td>
<td>.34</td>
<td>.03</td>
<td>.38</td>
</tr>
<tr>
<td>Fixation duration (msec.)</td>
<td>605</td>
<td>68</td>
<td>353</td>
</tr>
<tr>
<td>Error in fixating target (deg.)</td>
<td>.43</td>
<td>.08</td>
<td>.62</td>
</tr>
</tbody>
</table>
Pyridostigmine - Summary

The protocol for this agent called for the chronic administration of 7 mg/K of pyridostigmine to be given orally twice daily over a period of 14 days. Performance on Visual Search was collected periodically during the two weeks and compared to baseline sessions collected before and after the drug period. We did not detect any convincing abnormalities in neurological status, oculomotor competence or performance on the Visual Search test.

Respectfully submitted,

E. Gregory Keating, Ph.D.
Professor of Anatomy
Project Director

EGK:pic

cc: Capt. Thomas Harting
U.S.A.A.R.L.
P. O. Box 577
Fort Rucker, AL 36362
PYRIDOSTIGMINE - VISUAL SEARCH
PERCENT OF TARGETS FIXATED

\[ \text{Z Score} \]

\[ \text{DAY2} \quad \text{DAY4} \quad \text{DAY10} \quad \text{DAY11} \quad \text{POST} \]

\[ \text{SUBJECT 1} \]

\[ \text{SUBJECT 2} \]

MG/K

Figure 25
PYRIDOSTIGMINE - VISUAL SEARCH
PERCENT OF TARGETS FIXATED

EARLY

SUBJECT 3

Z SCORE

DAY2  DAY8  DAY10  DAY12  POST

+  +  +  +  +

MG/K

figure 26

+ - TO BE COLLECTED
PYRIDOSTIGMINE - VISUAL SEARCH
TIME TO FIND TARGET

SUBJECT 1

SUBJECT 2

MG/K
PYRIDOSTIGMINE - VISUAL SEARCH
TIME TO FIND TARGET

Z SCORE

SUBJECT 3

DAY 2  DAY 8  DAY 10  DAY 12  POST
+

MG/K

Figure 28
PYRIDOSTIGMINE - VISUAL SEARCH
NUMBER OF FIXATIONS TO FIND TARGET

 SUBJECT 1

 Z SCORE

 SUBJECT 2

 Z SCORE

 DAY2  DAY4  DAY10  DAY11  POST

 MG/K

 figure 29
PYRIDOSTIGMINE - VISUAL SEARCH
NUMBER OF FIXATIONS TO FIND TARGET

Z SCORE

DAY 2  DAY 8  DAY 10  DAY 12  POST

+ - TO BE COLLECTED

SUBJECT 3

M.G./K.
END
DATE
FILMED
9-88
DTIC