The Effects of Atropine Sulfate on Aviator Performance

By

Henry L. Taylor
John A. Dellinger
Bruce C. Richardson
Martha H. Weller
Stephen W. Porges
Christopher D. Wickens
James E. LeGrand
John M. Davis

Aviation Research Laboratory
University of Illinois at Urbana-Champaign

September 1989

United States Army Aeromedical Research Laboratory
Fort Rucker, Alabama 36362-5292

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Approved for public release; Distribution unlimited
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): ARL TR-85-1	5. MONITORING ORGANIZATION REPORT NUMBER(S): USAARL CR 89-9
6a. NAME OF PERFORMING ORGANIZATION: Aviation Research Laboratory, University of Illinois; 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): #1 Airport Road, Savoy, IL 61874	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: U.S. Army Medical Research & Development Command; 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-83-C-3150
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. 63764A; PROJECT NO. 3M4-63764D995; TASK NO. AA; WORK UNIT ACCESSION NO. 013

11. TITLE (Include Security Classification)

The Effects of Atropine Sulfate on Aviator Performance

12. PERSONAL AUTHOR(S) Henry L. Taylor, John A. Dellinger, Bruce C. Richardson, Martha H. Weller, Stephen W. Porges, Christopher D. Wickens, James E. LeGrand, John M. Davis

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
Final Report	FROM 83/5/15 TO 84/9/14	1989 September	77

16. SUPPLEMENTARY NOTATIO

n/a

17. COSATI CODES		
FIELD	GROUP	SUB-GROUP

18. SUBJECT TERMS (~~Continue on reverse if necessary and identify by block number~~)
Pilot performance, simulators, atropine sulfate, Sternberg task, chemical warfare, organophosphate compounds, instrument flight tasks. (TES)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)
The purpose of the present study was to determine the effect of atropine sulfate on pilot performance, as measured in a flight simulator, and to investigate physiological correlates of this effect. The six dependent measures of flying the simulator using standard instrument procedures indicated the significant effects of atropine and the time course of the effects. A monotonic increase in the effects of atropine was found between the 0.5 and the 4.0 mg levels of atropine. The most significant effect was due to the 4.0 mg level. For the Sternberg secondary task, reaction time and accuracy showed no atropine effects. Mean heart period (MHP), heart period variance (HPV), and (RSA amplitude), showed the effects of atropine sulfate and the time course of the effect. It was concluded that the 4.0 mg level of atropine produced significant performance decrements and increased the risk of error when performing complex pilot tasks. The performance effects were found to lag the physiological effects. Operational implications of the time lag were discussed.

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	Unclassified
22a. NAME OF RESPONSIBLE INDIVIDUAL: Mrs. Virginia Miller	22b. TELEPHONE (Include Area Code): 301-663-7325; 22c. OFFICE SYMBOL: SGRD-RMS

EXECUTIVE SUMMARY

The threat of the use of organophosphorous compounds in chemical warfare has implications for the safety of military pilots. Military personnel in high threat environments are issued atropine for self administration as an antidote. Both the toxic chemical compound and the antidote can pose serious problems for the pilot. Previous investigators have recommended 2-mg atropine sulfate injections for subjects with suspected poisoning by a chemical agent, but they reported that 5-mg injections in the absence of such poisoning might produce significant side effects. They found that the first sign of the effects of atropine was bradycardia followed by an increase in heart rate. In studies using higher levels of atropine (up to 12.95 mg), clinical symptoms have been described as a parasympathetic block, manifested by symptoms such as tachycardia and dryness of the mouth, followed by diffuse central nervous system effects of longer duration (typically 10-12 hours). They found that the effective dose of atropine sulfate that increased heart rate was 1.32 mg and the ED50 that decreased cognitive performance was 4.71 mg. The physiological effects appeared and disappeared more quickly than the performance decrements. In another study, performance impairment in routine tasks was found 3 1/4 hours after final injection.

The U.S. Army has authorized soldiers to carry three auto-injectors each containing 2 mg of atropine sulfate. In the event of a suspected anticholinesterase exposure, military personnel are instructed to 2 mg intramuscularly and to repeat the injection 20 minutes later if they are not experiencing the effects of atropine (e.g., tachycardia and dry mouth). Therefore, it is possible that up to 4 mg of atropine sulfate may be used by a military aviator who suspects exposure, but was not exposed to an organophosphate agent.

While previous experimenters have adequately described gross performance effects of atropine, an evaluation was needed to determine the effects of atropine sulfate on the performance of complex psychomotor tasks in aviators. The use of flight simulators to collect data on the effects of drugs on pilot performance was attractive. The purpose of the present study was to examine the effect of atropine sulfate on pilot performance and to investigate physiological correlates of this effect. Flight simulator performance, Sternberg task performance, and subjective assessments of pilot errors were used to examine the performance effects. To assess the physiological effects of atropine, changes in electrocardiogram (ECG) and subjective symptoms were recorded. Heart period and heart period variation information was derived from the ECG recordings, and the variance within the heart periods was partitioned into an estimate of RSA amplitude ($\hat{V}$).

Method

The equipment used to collect flight performance data during instrument flight rules (IFR) flight consisted of a fixed-base flight simulator with its own digital computer. A second computer was used to record digital performance data and to drive a speech synthesizer to generate and present auditory stimuli to the simulator cockpit.

Twenty healthy, male general aviation pilots ranging in age from 19 to 30 years (mean 22 years) served as subjects. The flight experience ranged from 112 to 1150 flying hours with a mean of 307 hours experience. Simulator experience for the subjects ranged from 5 to 100 hours; nineteen subjects each had at least 19 hours of experience, with a mean of 37 hours.

The experimental scenario included a primary task, flying the simulator using standard instrument flight procedures; and a secondary task, the Sternberg choice reaction time task. The primary task was representative of tasks that pilots typically perform when flying under IFR conditions. The secondary task was representative of communication tasks that increase workload by requiring the pilot to receive, understand, and respond to verbal information.

The primary task consisted of a direct entry to a holding pattern, the execution of three holding patterns, and a simulated Instrument Landing System (ILS) approach. Throughout the primary task, the flight parameters of altitude, rate of turn, localizer, and glideslope tracking were sampled at 1 Hz by the computer. During the flight, the Sternberg task was randomly presented as a secondary task to increase the workload of the subject.

Physiological recordings of five minutes of ECG and respiration data were recorded following each simulator flight. After the physiological recording session, subjects answered a 13-item symptoms checklist.

The experimental sessions included simulator flights and physiological recording periods alternating on 20-minute cycles for three hours post-injection. Four-hour experimental sessions were scheduled one week apart for seven consecutive weeks. The subjects completed two training sessions which acquainted them with holding procedures, ILS approaches, and the Sternberg task. The first atropine sulfate injection was given during the third session.

Four levels of atropine sulfate and a placebo were administered to each of the 20 subjects over the course of five experimental sessions. A five by five Latin Square design was used to balance drug order effects. There were four subjects per group and each group had a different treatment schedule.

All drugs were administered according to subject weight. The subjects received atropine injections of 0, 0.006, 0.013, 0.026, and 0.053 mg/kg, which corresponded, respectively, to the 0, 0.5, 1.0, 2.0, and 4.0 mg/75 kg treatment conditions.

The first flight for each experimental session served as a baseline flight. Following the first flight, the appropriate level of atropine sulfate was administered during the rest period after baseline physiological data had been collected. Performance data on the primary and secondary tasks were collected for the remaining five flights. ECG and respiration rate were recorded during the rest periods following the remaining five flights. All data were collected under double blind conditions.

A Latin Square within subjects, repeated measures analysis was used for statistical analysis. This plan assumes that treatment, experimental session, and flight are fixed effects and that subjects within the groups is a random variable.

Results

Six root mean square (RMS) deviation values were computed from simulator flight data: altitude error while straight and level (ALT1); altitude error while turning (ALT2); turning rate control while straight and level (TC1); turning rate control while turning (TC2); localizer (lateral) tracking error (LOC); and glideslope (vertical) tracking error (GS).

The mean RMS errors were plotted as a function of time (flight) for each of the six primary task dependent variables for the five treatment conditions. The predominant treatment effect was the time course of the 4.0 mg/75 kg treatment condition. For all dependent variables, the increased mean RMS error for the 4.0 mg treatment condition was apparent for the second post-injection flight (time 1:00) and continued to increase or to remain essentially the same throughout the remainder of the experimental session. There appeared to be no difference between the control and the 0.5 and the 1.0 mg treatments. The 2.0 mg treatment condition showed increased RMS error for some time periods and variables.

A multivariate analysis of variance (MANOVA) was used to test the main effects and the first order interaction effects. An approximate F-Test, based on Wilks' Criterion, indicated a significant treatment main effect, but session and group were not significant. The treatment x flight interaction was significant, but other interaction effects were not significant.

An analysis of variance (ANOVA) showed significant treatment effects for each of the six primary task dependent variables. Linear contrasts between the control and each of the four treatment levels of atropine indicated that the treatment effect was primarily due to the 0-4 contrasts, which were significant for all six dependent variables. The contrast between the control and the 2.0 mg treatment level for altitude control while turning was significant. The main effect of flight was significant for five of the primary task dependent variables (LOC was the only exception). The treatment x flight interaction was significant for four primary task dependent variables.

MANOVAs for each flight showed that the treatment main effect was significant for flights 3, 4, 5, and 6, but not for flights 1 and 2. ANOVAs for each of the six primary task dependent variables for each flight indicated no significant differences for any of the dependent variables for flights 1 and 2, but significant differences were found for three of the primary task dependent variables for flights 3, 4, 5, and 6, and for the other three variables for at least the last flight. Contrasts were computed between the control and each of the other treatment conditions. The primary loci of the performance decrements are in the 0-4 contrasts.

Standardized RMS scores for five of the six primary task dependent variables showed a monotonic increase from the 0.5 to the 4.0 mg treatment level for the fifth flight.

Tracings of lateral tracking for the holding and approach phases of the simulator flight task were scored for "procedural" and "fatal" errors. Due to lack of inter-rater reliability, the results of the "procedural" and "fatal" error analysis were not included.

The overall intrusiveness of the Sternberg task on the primary task was tested and found to be minimal. The findings also indicate that performance on the Sternberg task did not differ between drug treatment levels.

Percent accuracy and reaction times were plotted. Compared to the approach phase, higher accuracy and faster response times were found for the holding phase for both positive set sizes, 2 and 4; the data lie in completely non-overlapping clusters. The data indicate that the Sternberg task was a good secondary task. The random pattern of data for the 2 and 4 positive set size and across the different treatment levels within the approach and the holding phases clearly indicates that there were no speed-accuracy trade-offs as a function of treatment level.

The mean true and false reaction times for the five post-injection flights were plotted as a function of positive set size (2 and 4) for each of the treatment levels. No treatment effects were found during either the holding or approach phases. During the

holding phase, the slopes for the true reaction times were positive and the true reaction times were faster than the false reaction times. These results are consistent with the Sternberg model. The negative slopes of the false reaction times for the holding phase, however, are not consistent with the Sternberg model.

An ANOVA indicated that there was no treatment main effect for the reaction time variable, nor were the flight, positive set size, group or period main effects significant. The true-false main effect was significant and the true-false x positive set size interaction was significant.

The ECG data were digitized and the mean heart period (MHP), the heart period variance (HPV), and $\hat{V}$ were computed. The $\hat{V}$ and the HPV were transformed using a natural logarithm transformation to normalize the distributions. Means for the MHP, HPV and $\hat{V}$ distributions were computed for each treatment condition for each of the six physiological recording periods.

The means for the heart period data revealed that there was a decrease in MHP for the 4.0, 2.0, and 1.0 mg treatment conditions for the first post-injection time period (:35). The peak effect for the 4.0 mg treatment condition occurred during this period and was followed by a gradual recovery which was still in progress at the end of the experimental session. The time course of the 2.0 mg treatment condition was similar. The peak effect of the 1.0 mg treatment condition occurred during the second post-injection period (1:15) followed by a gradual recovery which was complete by the fifth post-injection period (3:15). The 0.5 mg treatment condition showed an *increase in the mean heart period followed by a recovery.*

The HPV and $\hat{V}$ means indicated similar dose-response time trends for the 4.0, 2.0, and 1.0 mg treatment conditions as those observed for the MHP treatment. The means for the 0.5 mg treatment condition were not significantly different from the control mean for any of the post-injection time periods for either HPV or $\hat{V}$.

ANOVAs for MHP, HPV, and $\hat{V}$ indicated that the main effects of treatment and time were significant as was the treatment x time interaction, but the group and experimental session main effects were not significant. ANOVAs, computed for each post-injection time period for each dependent variable, indicated that each post-injection time interval was significant for each of the three dependent variables. Linear contrasts between the control (0) and the 2.0 mg and between the control and the 4.0 mg treatment conditions for all three dependent variables were significant for all post-injection time periods, which indicated that the MHP, HPV, and $\hat{V}$ all failed to return to the control level. The 0-1 contrasts were significant for the first three post-injection periods for HPV and for the second, third, and fourth post-injection periods for MHP and $\hat{V}$. The 0-1 contrasts

were not significant for the final post-injection period for any of the three dependent variables, which indicated recovery for all three dependent variables at 3:15 post-injection for the 1.0 mg treatment condition. None of the contrasts were significant between the 0 and 0.5 mg treatment conditions for HPV and $\hat{V}$ and only the first contrast for the :35 post-injection period and the last (3:15) for MHP. The first contrast was the result of a significant increase in the MHP. The 0.5 mg treatment condition had no significant effect on HPV or $\hat{V}$.

The ED50s of the atropine for the three dependent variables were estimated using probit analysis. The quantal response used as the criterion was a 30% decrease in MHP, HPV, or $\hat{V}$. The number of individuals that had a 30% decrease for each treatment level was used for the probit analysis for each dependent variable. The ED50s of atropine for the 30% decrease were:

(a) MHP = 2.52 mg ($\chi^2(2, N=4) = 2.57, p=.28$);

(b) HPV = 1.61 mg ($\chi^2(2, N=4) = 6.58, p=.04$); and

(c) $\hat{V}$ = 0.98 mb ($\chi^2(2, N=4) = 1.21, p=.55$).

When the ED50s of the three dependent variables were compared, RSA amplitude ($\hat{V}$) was the most sensitive indicator of the vagolytic effects of atropine sulfate.

ED50s were estimated for 6 symptoms using probit analysis. The ED50 estimate for the symptom, "Dry Mouth," was 0.34 mg; "Difficult to Swallow," 2.11 mg; "Hard to Read Checklist," 3.29 mg; and "Fluttery Chest," 5.07 mg of atropine. All estimates provide a good fit to the estimated probit line. Good fits to the probit line estimate were not obtained for "Racing Heart", with an estimated ED50 of 2.58 mg; and for "Lights Bright," with an estimated ED50 of 4.28 mg.

Nineteen of the twenty subjects completed a post-participation questionnaire. All persons receiving 4.0 mg of atropine sulfate perceived the effects. About two-thirds complained of visual problems; approximately one-third complained of dizziness, headache, fatigue, and confusion; eleven (59%) reported that the symptoms were worse than expected and would not participate in a similar experiment again. The side effects of the 4.0 mg treatment level were felt for an average of 14 hours with a range of 2 to 48 hours reported.

Discussion

The results from the primary task dependent measures clearly indicated the effects of atropine on pilot performance. The 4.0 mg

treatment condition consistently resulted in performance decrements for flight tasks observed. Some performance decrements occurred for the 2.0 mg treatment level, but these decrements appeared later, were not as consistent across flight tasks, and generally persisted for a shorter time duration compared with 4.0 mg. No substantial primary task performance decrements should be expected for the 0.5 and the 1.0 mg treatment conditions.

A comparison of the six primary task dependent variables at the 2:20 post-injection time period indicated that five of the variables showed a monotonic increase in mean RMS error (reduced performance) as the level of atropine was increased beyond 0.5 mg, demonstrating the orderliness of the dose-response of atropine. The present study has clearly demonstrated that RMS error for altitude and heading control while both straight and level and turning, and for dual task tracking is effective in detecting the dose-response effects of atropine over time.

Some performance decrement should be expected within 1:40 after injecting 2.0 mg of atropine and the substantial performance decrements that occur within 1:00 hour of a 4.0 mg injection should be expected to continue for over two hours. The performance decrements related to atropine were compared to known performance decrements from alcohol. Probit analysis indicated that the estimated ED50 for the level of atropine equivalent to the decrement found for the 0.082% BAL ethanol level was 3.12 mg of atropine sulfate; a very good fit to the probit line estimate was found. These data indicated that in fifty percent of the pilots, the performance decrement caused by a 3.0 mg injection of atropine will be similar to that caused by a 0.082 BAL.

The Sternberg task clearly fulfilled its role as a secondary task, loading the pilot's residual capacity. This loading was most clearly demonstrated by the differences in Sternberg task performance between the holding and approach phases. Interestingly, despite the pronounced effects of drug treatment on the primary flight task, drug treatment failed to show any influences on the Sternberg task. The most likely hypothesis to explain this lack of effect is simply that atropine sulfate failed to influence the cognitive processes involved in performing the Sternberg task.

The MHP, HPV and $\hat{V}$ data clearly indicated the physiological effects of atropine sulfate and the time course of the effect. The decrease in MHP for the 4.0, 2.0, and 1.0 mg treatment conditions observed during the first post-injection recording period (:35) was expected. Other investigators have reported an early onset of rapid tachycardia. The MHP data for the 0.5 mg treatment level showed the expected bradycardia followed by recovery. As had been previously reported, higher atropine levels resulted in rapid parasympathetic effects, indicating rapid blocking of the vagal influence on the heart.

As expected, the dose-response relationships for performance effects, physiological effects and symptoms varied significantly among the individual subjects. Probit analysis provided estimates that account for individual differences. The estimate of the atropine level at which 50% of the population will experience a 30% decrease in MHP was 2.52 mg of atropine. The estimate for a 30% decrease for HPV was 1.61 mg of atropine and the estimate for $\hat{V}$ was 0.98 mg of atropine. These findings appear to support the conclusions of previous investigators that $\hat{V}$ is sensitive to changes in the vagal influence on the heart and responds in a different manner than MHP and HPV. Clearly, these findings indicate that $\hat{V}$ is a more sensitive measure of the vagolytic effects of atropine sulfate than either MHP or HPV.

The use of probit analysis to rank order subjective symptoms and to give estimates of ED50s is informative. After injecting 0.5 mg of atropine sulfate, one can expect 50% of the population to experience dry mouth and 1 mg will produce the same effect for a longer duration. The 2.0 mg level will produce difficulty in swallowing and some complaints of tachycardia. The 4.0 mg level will produce higher incidences of the lower dose symptoms plus visual effects that may be very significant to aviators.

The use of atropine sulfate during complex task performance is not normally recommended. However, in the case of military pilots who are required to operate in a high risk chemical warfare environment, auto-injection and/or pretreatment with atropine sulfate may be essential to survival. A single 2.0 mg atropine self-injection is expected to result in some reduced ability to perform complex pilot tasks, and should be used only when there is a very high probability of exposure. A 4.0 mg injection was found to produce significant performance decrements and to clearly increase the risk of error when performing complex pilot tasks.

The difference in the time course of the dose-response relationships for performance decrements, physiological response and symptoms was one of the most interesting findings of the present study. This finding also appears to provide information of potential operational significance for the use of atropine sulfate among Army aviators. The performance decrements for the 2.0 mg atropine level ere not significant until 1:40 post-injection. At the 4.0 mg level of atropine, the performance decrements were significant at 1:00 post-injection. On the other hand, the physiological effects were noted at :35 post-injection. Unlike the immediate parasympathetic effects (i.e., dry mouth and tachycardia), the performance decrements lag considerably.

This lag in performance decrements when compared to the physiological symptoms may permit the military pilot who injects atropine sulfate, but has not been exposed to a chemical agent, time

to land safely. With higher levels of atropine, however, the lag between atropine injection and physiological performance effects is reduced. If an Army aviator injects 4.0 mg of atropine and experiences the effects of atropine (e.g., tachycardia and dry mouth), it is expected that performance decrements will follow. The physiological symptoms can be used as an alerting signal to the aviator.

FOREWORD

For the protection of human subjects the investigators have adhered to policies of applicable Federal Law 45CFR46.

ACKNOWLEDGMENTS

This research was supported by Contract No. DAMD17-83-C-3150 from the U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, Maryland. Captain Bruce E. Hamilton and Mr. Ronald R. Simmons were the Contracting Officer's Technical Representatives. We are endebted to F. Hyman, D. Palmer, and R. Braune for performance data collection; to K. Gaddis, S. Lyness, and Y. Izumi for physiological data collection and analysis; to the thirteen nurses for medical monitoring; and to the twenty student pilots who served as subjects. A thesis based on the results of this research was accepted by the Graduate College at the University of Illinois at Urbana-Champaign in partial fulfillment of the requirements for the degree of Doctor of Philosophy for John A. Dellinger.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF FIGURES (continued)

INTRODUCTION

The threat of the use of organophosphorous compounds in chemical warfare has implications for the safety of military pilots. Many chemical agents are strong neurotoxins that can be lethal in small amounts and detrimental to psychomotor performance in minute chronic exposures. Therefore, military personnel in high threat environments are issued atropine for self administration as an antidote. Both the toxic chemical compound and the antidote can pose serious problems for the pilot.

Acute exposure to an organophosphorous compound results in the inhibition of acetycholinesterase (AChE) which in turn results in accumulation of acetylcholine (ACh) at the neural synapses. The accumulation of ACh, a neurotransmitter, causes cholinergic receptors to be overstimulated. In fatal exposures, death is caused by respiratory paralysis in conjunction with central nervous system (CNS) depression (1).

Antidotal drugs can be used either as a therapeutic or as a pretreatment. Therapeutic treatment of AChE inhibition requires that anticholinergic drugs such as atropine sulfate be administered immediately following exposure to combat the muscarinic symptoms. Atropine sulfate penetrates in the CNS and antagonizes the excess ACh. Goldstein et al. (1) noted that atropine acts on the parasympathetic effector organs and the CNS, but that there is practically no antagonistic effect at the neuromusuclar junctions.

In clinical settings atropine sulfate is prescribed in doses up to 1 mg. After acute exposure to organophosphorous compounds, an individual's tolerance to atropine is increased, and up to 50 mg may be used the first day to combat the muscarinic symptoms (2). The physiological symptoms and gross behavioral effects of atropine sulfate have been studied in man. Cullumbine, McKee and Creasey (3) evaluated the effects of administering 2 to 5 mg of atropine sulfate to normal healthy subjects and concluded "that 2 mg. atropine sulfate can be recommended for injection into subjects with suspected poisoning by an anticholinesterase, but that 5 mg. in the absence of such poisoning may produce embarrassing effects" (p. 318). They reported that, in many individuals, the first sign of the effects of atropine was bradycardia followed by an increase in heart rate.

The comparative pharmacology of atropine, scopolamine and ditran has been investigated by Ketchum, Sidell, Crowell, Aghajanian, and Hayes (4). Their study concentrated on the effects of the higher doses of atropine (up to 12.95 mg). The clinical symptoms were described as a parasympathetic block, manifested by symptoms such as tachycardia and dryness of the mouth, followed by diffuse CNS effects of longer duration (typically 10-12 hours). They found that, in a 74

kg person, the effective dose of atropine sulfate that increased heart rate by 30% in 50% of the subjects (ED50) was 1.32 mg. The ED50 that decreased cognitive performance on the Number Facility test by 25% was 4.71 mg. The cardiac effects appeared and disappeared more quickly than the performance decrements on the Number Facility test. An increase in heart rate was also observed by Sawka et al. (5) who reported the peak cardiac response at 70 minutes post-injection using 0.5 to 4 mg of atropine.

Moylan-Jones (6) evaluated the behavioral effects of three 2-mg injections (each 20 minutes apart) by observing routine tasks (i.e., hard labor, map reading and compass bearings, rifle shooting and tire changing) and the Number Facility task. In most of the 23 subjects studied, he found some degree of performance impairment 3 hours and 15 minutes after administration of the final injection.

The U.S. Army has authorized soldiers to carry three auto-injectors each containing 2 mg of atropine sulfate (5). In the event of a suspected anticholinesterase exposure, military personnel are instructed to inject 2 mg intramuscularly and to repeat the injection 20 minutes later if they are not experiencing the effects of atropine (e.g., tachycardia and dry mouth). Therefore, it is possible that up to 4 mg of atropine sulfate may be used by a military aviator who suspects exposure, but was not exposed to an organophosphate agent.

While previous experimenters have adequately described gross behavioral effects of atropine, an evaluation is needed to determine the effects of atropine sulfate on the performance of complex psychomotor tasks in aviators. The use of flight simulators to collect data on the effects of drugs on pilot performance is attractive. Billings, Gerke, and Wick (7) orally administered secobarbitol and compared performance in flight to performance in a ground simulator. They found the magnitude of errors to be smaller but more consistent in the flight simulator than in the aircraft. They concluded that the flight simulator provided a sensitive means by which to study the effects of drug stress on pilots. Flight simulators have been used by a number of investigators to study the effects of ethanol on pilot performance (8, 9, 10, 11, 12). Performance decrements have been found at moderate blood alcohol levels (.05 BAL and above). Flight simulators have also been used to study the effects of marijuana (13) and anti-emetic drugs (14).

The root mean square (RMS) deviation or tracking error has been used as a dependent measure for determining the effects of drugs on pilot performance in the flight simulator (15). Computation of an RMS error is similar to computing a standard deviation except that a targeted value is substituted for the parameter mean. Following a review and analysis of RMS errors, Kelley (16) concluded that with

respect to measuring error amplitudes, RMS error was the best single measure.

Performance on flight simulator tasks, such as instrument flight procedures, is likely to be relatively automatic in a well-trained pilot and mental resources may not be fully used. Under drug stress, it has been assumed that subjects shift to other resources to compensate for drug effects (17). A secondary task can be used to increase task difficulty. The Sternberg task, a choice reaction time task involved with short-term memory, was selected as a secondary task for the current study for the following reasons:

1. A performance model had been developed which allowed the diagnosis of effects on specific cognitive processes (18).

2. The task had been successfully used for toxicant studies (17, 19).

3. The task had been used in dual task performance assessment (20, 21, 22).

4. The task, which in the present study used an auditory stimulus and manual response, was expected to have high face validity as a communications task for pilots.

Sternberg assumed that more complex choices take longer to process mentally and that the mean reaction time (RT) is a linear function of the number of available alternatives or positive set size (23). He (18) also assumed that the factors that make up the mean RT are additive. He described four processing stages involved in evaluating the test probe and responses: (a) stimulus encoding, which depends on the clearness of the test probe presentation; (b) a serial and exhaustive memory search through the elements of the positive set; (c) a binary decision of "true" or "false" for the correct response; and (d) the translation and organization of the answer into a response.

The Smith and Langolf (17) and Osborne and Rogers (19) studies used the Sternberg task as a single task. The primary goal of the present study was to examine pilot performance. Therefore, the Sternberg task was used in a dual task situation with the primary task being flight simulator performance. When subjects time-share in dual task situations, emphasis may be switched between the tasks as a result of changes in task difficulty or because of changes in mental processes that result from the drug effect. Responses to the Sternberg task are scored for reaction time and accuracy and are potentially susceptible to speed and accuracy trade-offs.

The final reason for selecting the Sternberg task was its high face validity to the pilot subjects. Ogden et al. (24) pointed out

that operator acceptance and high face validity were important to many secondary task situations. The Sternberg task is similar to normal operating procedures whereby the pilot monitors the radio for pertinent communications and then responds to those that are considered relevant. Wolf (25) used the Sternberg task with flight simulator performance to evaluate pilot workload. He used the task to increase the overall workload and to enhance methodological sensitivity.

In addition to evaluating the effects of toxic substances on pilot performance, we are interested in evaluating the physiological correlates of these effects. Time correlates; mean heart period (MHP), or the mean of the beat-to-beat intervals; and heart period variance (HPV), or the change in sequential beat-to-beat intervals over time, have been extensively investigated. The relationship between respiration and phasic modulation of the vagal influence on the heart, known as respiratory sinus arrythmia (RSA), is also well known. Non-invasive methods for measuring RSA have been developed in order to estimate vagal influence on the heart. Porges, McCabe and Yongue (26) reported that vagal control of the heart can be estimated by analyzing the mean heart period and heart period variability associated with the normal respiratory frequency band. They derived a measure of RSA, $\hat{V}$, which is the amplitude of the heart period variance corresponding with normal respiration (i.e., 0.12 to 0.40 Hz).

Yongue et al. (27) used atropine methylnitrate and phenylephrine to pharmacologically manipulate the $\hat{V}$ estimate of RSA in rats. Atropine methylnitrate produced a peripheral block of the vagus and decreased RSA, while phenylephrine elevated RSA indirectly by hypertensive effects. McCabe, Yongue, Porges, and Ackles (28) studied the relationship between RSA and the vagus in rabbits by manipulating vagal tone with aortic nerve stimulation. They concluded that "$\hat{V}$ is sensitive to manipulations of vagal influences on the heart," and that it often responded "in a different manner than heart period or heart period variance" (p. 149). Porges and his colleagues studied the use of RSA for monitoring levels of anesthesia (29) and for evaluating stress (30).

Dose-response relationships of toxic compounds normally vary widely among individuals and this variability must be taken into account when investigating drug effects. The classical dose-response relationship is sigmoid in form. Quantal (all-or-none) dose-responses such as lethality are normally distributed and the percent response can be converted to a standardized unit of deviation from the mean of the normal distribution. In toxicology, these units of deviation have been termed normal equivalent units of deviation (NED). The NED scale is a Z score scale with the mean (50% response) equal to 0 and + 1 NED equal to 84.1 percent response; while - 1 NED is equal to 15.9 percent response. The NED scale can be converted to the probit (probability unit) scale by adding + 5 to the NED scale. Thus, the mean of the

probit scale equals 5 and the standard deviation equals +/- 1. The logarithm dose of the drug can be plotted as a function of percent cumulative response using a probit scale. Probit analysis is commonly used in toxicology for estimating typical relative dose-response relationships.

If the criterion response is lethality, the lethal dose resulting in 50% mortality (LD50) will be equal to 5 on the probit scale; if the criterion is a graded response, an effective dose resulting in 50% response (ED50) will equal 5 on the probit scale.

Atropine sulfate doses above 1.0 mg are expected to result in monotonic responses within individuals. However, below 1.0 mg, opposite responses to atropine are expected, such as increased heart periods at low doses as reported by Cullumbine et al. (3). The treatment effects above 1.0 mg are likely to result in decrements in complex performance. Graded responses by individuals may be converted to quantal response (all-or-none) by referring to a specific graded response level as the criterion. For example, mean heart period may be analyzed by counting the number of subjects at each dose level who had more than a 30% decrease in heart period. The use of graded responses as quantal responses in probit analysis is acceptable according to Klaassen and Doull (31).

Sidell and Pless (32) used probit analysis in a study of the effects of ethanol to determine the relative ED50 for subjective, physiological, and behavioral symptoms. They found the technique particularly useful because some subjects responded with "severe" symptoms on some items, although few items were marked consistently. Using probit analysis, Sidell and Pless (32) were able to rank order the symptoms from "sleepy" (ED50 = 0.6 mg/kg) to "altered speech" (ED50 = 1.7 mg/kg) (p. 258). Probit analysis was used similarly in the present study to analyze responses to a subjective symptoms checklist.

The purpose of the present study was to examine the effect of atropine sulfate on pilot performance and to investigate physiological correlates of this effect. Flight simulator performance, Sternberg task performance, and subjective assessments of pilot errors were used to examine the performance effects. To assess the physiological effects of atropine, changes in electrocardiogram (ECG) and subjective symptoms were recorded. Heart period and heart period variation information was derived from the ECG recordings, and the variance within the heart periods was partitioned into an estimate of RSA amplitude.

METHOD

Equipment

The equipment used to collect flight performance data consisted of a fixed-base flight simulator, ILLIMAC 2, an acronym for ILLInois Micro Aviation Computer. The simulator was modeled after the ILLIMAC engineering prototype simulator which was described in detail by Taylor, Staples, Todd, and Harshbarger (33). Both the ILLIMAC engineering prototype and ILLIMAC 2 were designed and developed by Aviation Research Laboratory (ARL) personnel at the Institute of Aviation, University of Illinois at Urbana-Champaign. In building ILLIMAC 2, ARL personnel used the shell, base and rudder pedals of a commercially available general aviation trainer (Figure 1). The instrumentation, computer and electronic components were designed and constructed by ARL personnel.

The ILLIMAC 2 computer consists of a microprocessor section, a special function section, and an input/output (I/O) section. The microprocessor section contains three boards: a Microprocessor board with an 8086 chip, a PROM/RAM board that contains 32K bytes of memory, and an Address Decode and Clock Frequencies board. The special function section consists of an Array Processor board, a Trigonometric Digital/Analog (D/A) board and a Trigonometric Look-Up Tables board. The Array Processor board enables the single microprocessor to perform simulation functions at a 30-HZ rate. The input/output section contains twelve printed circuit boards that control I/O functions between the cockpit and the computer. These boards drive all analog functions in the cockpit, and receive digital and analog information from the cockpit.

The ILLIMAC 2 simulates the flight characteristics of a complex, high performance, single engine aircraft. The ILLIMAC 2 flight panel, shown in Figure 2, contains the instrumentation and navigation/communication equipment to facilitate instrument flight rules (IFR) approaches. The navigational facilities and airports within a 512 mile (824 km) by 512 mile (824 km) area centered around the University of Illinois-Willard Airport are programmed in the computer. The ILLIMAC 2 system includes an X-Y flight path recorder (Figure 3) capable of horizontal or vertical tracings that can be used to record approaches to terminal facilities.

A commercially available 8086 computer with two eight-inch floppy disk drives and a CRT (Figure 4), connected to the ILLIMAC 2 by an RS-232C line, was used to record digital performance data generated during flight. The computer drove a speech synthesizer to generate and present auditory stimuli to the ILLIMAC cockpit.

Figure 1. ILLIMAC (ILLInois Micro Aviation Computer) flight simulator used for the primary task.

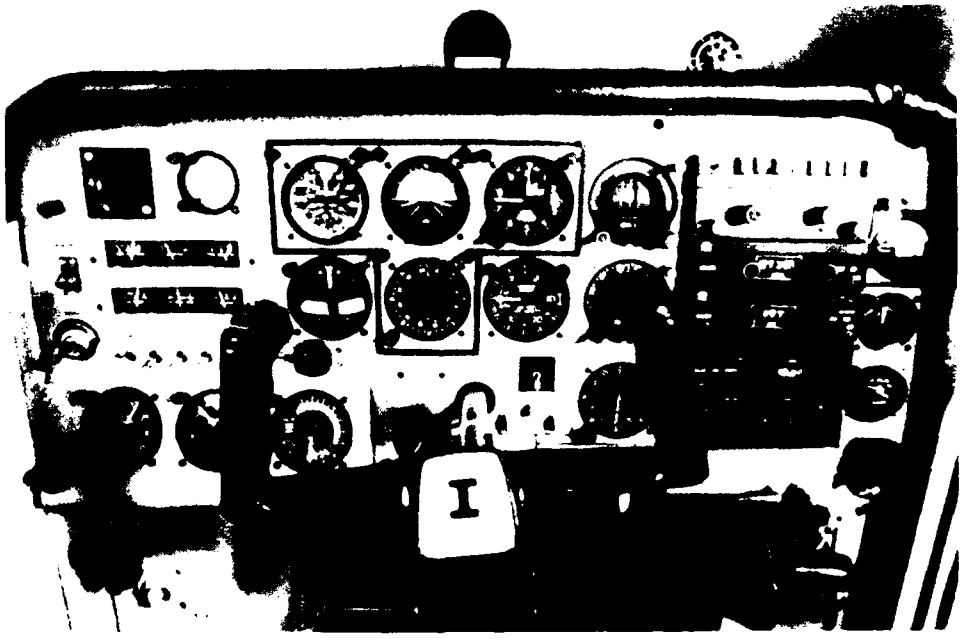


Figure 2. ILLIMAC flight panel.

Figure 3. ILLIMAC flight path recorder.

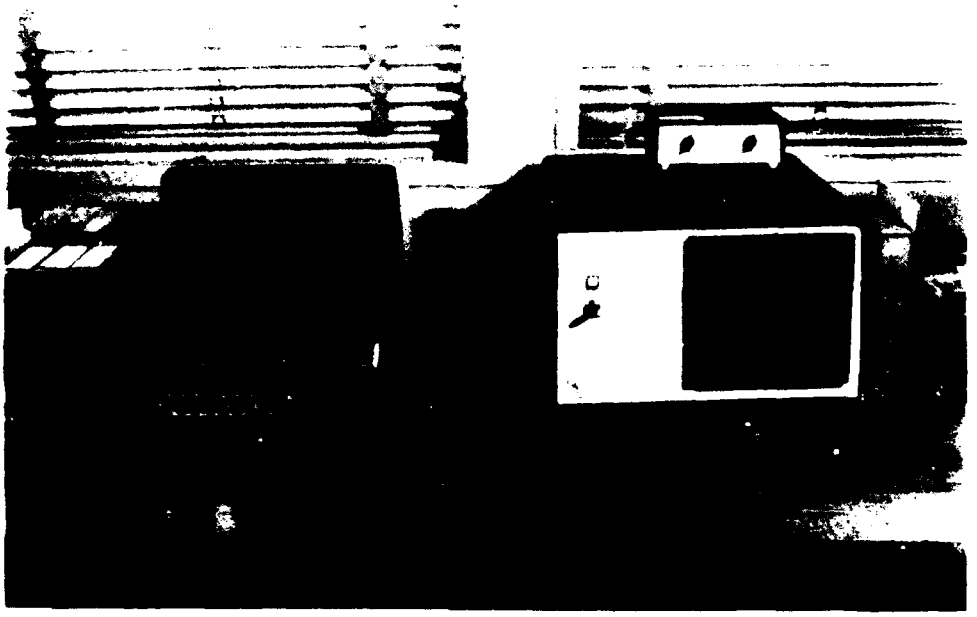


Figure 4. 8086 Microcomputer with CRT.

A thoracic expansion belt was used to record respiratory cycles. Standard ECG equipment, with three biopotential silver-silver chloride electrodes, was used to record cardiac electrical potentials. These data were amplified and stored on magnetic tape using an FM tape recorder (Figure 5). A separate mini-computer was used to convert heart period data into beat-by-beat periods to the nearest msec and to sample respiration twice per second.

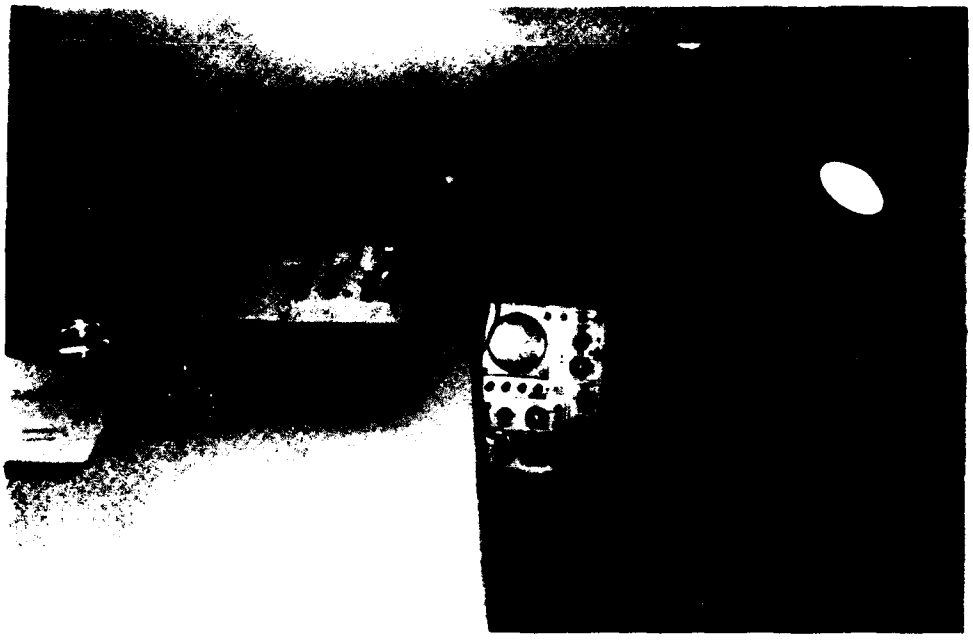


Figure 5. Equipment used to amplify and record the electrocardiogram (ECG) and respiration signals.

Subjects

Twenty male general aviation pilots ranging in age from 19 to 30 years (mean 22 years) with no medical problems (FAA Class 2 Medical Certificates) served as subjects. The subjects ranged in weight from 61.2 to 107.2 kg (mean 76.9 kg). They were paid volunteers from University of Illinois aviation courses who had received commercial and instrument pilot training. The flight experience for the twenty subjects ranged from 112 to 1150 flying hours with a mean of 307 hours experience. All subjects had a minimum of 19 hours in flight simulators with the exception of one subject who had 5 hours of previous flight simulator experience. This subject, an instrument-rated pilot with 55 hours of instrument time, demonstrated acceptable simulator proficiency prior to acceptance into the study. Simulator experience for the remaining nineteen subjects ranged from 19 to 100 hours with a mean of 37 hours.

The subjects were selected on the basis of previous flight instruction, scheduling availability, and medical screening. All were fully informed of the purpose of the study, the amounts of atropine sulfate to be administered, risks associated with the study, scheduling responsibilities, testing procedures, and wages. They were not informed of the sequence of drugs and were randomly assigned to a given treatment group. The subjects' intake of drugs and medication was checked at the time of the physical examination used in screening subjects, as well as immediately before each experimental session. They were warned not to drink alcohol the night before the experiment, which could have dehydrated them and increased their discomfort.

During the session, the subjects were under constant observation by either a Registered Nurse (RN) or a Certified Flight Instructor (CFI). The nurse drove the subject home after each session. All subjects agreed not to fly solo for 24 hours after participation. An emergency kit with oxygen was available at the experimental site to provide resuscitation equipment and medication in the event of a medical problem.

The use of human subjects in this project was reviewed and approved by the University of Illinois' Institutional Review Board (IRB) and the U.S. Army's Human Use Review Office. Each subject signed a consent form approved by the IRB. Each subject received a pre-experimental physical including an ECG and test for glaucoma; each subject was scheduled for a post-experimental physical.

Procedures

Experimental Scenario. The experimental scenario has been used by ARL investigators to determine the effects of toxic compounds on pilot performance (12, 14, 15). The scenario included a primary task,

flying the simulator using standard instrument flight procedures, and a secondary task, the Sternberg choice reaction time task. The primary task was representative of tasks that pilots typically perform when flying under IFR conditions. The secondary task was representative of communication tasks that increase workload by requiring the pilot to receive, understand, and respond to verbal information.

Experimental Sessions. The experimental sessions included simulator flights and physiological recording periods alternating on 20-minute cycles as shown in Table 1. Each experimental session began with a medical check when the RN asked questions about eating and sleeping habits during the previous 24 hours and determined baseline pulse and blood pressure readings. After the medical check-in, the subject flew one 20-minute simulator flight to provide baseline data. During the next 20 minutes, the subject was checked medically, physiological data were collected, and then the subject received the appropriate atropine sulfate injection. In order to follow the time course of the effects of atropine, flight data and physiological data were collected during the remaining flight and medical check periods, respectively, for three hours post-injection.

Four-hour experimental sessions were scheduled one week apart for seven consecutive weeks. The subjects completed a minimum of two training sessions before the treatment sessions began. The two training sessions acquainted the subjects with holding procedures, ILS approaches, and the Sternberg task. The first experimental session was used as an orientation and training session. Each subject was tested for the ability to perform the primary task within the limits set by the Federal Aviation Administration (FAA) in the Flight Test Guide for Instrument Pilot Candidates (34). The following limits were used: altitude deviation, +/- 100 ft. (30.5 m); horizontal tracking deviation (localizer), +/- 1.5 degrees; vertical tracking deviation (glideslope), +/- 0.7 degrees; and rate of turn, 6 degrees per second. Flight data were sampled once per second and the percent of samples outside the prescribed limits (% out) were determined. Performance during the second training session was considered acceptable if the subject had less than 1% of the sample outside the prescribed limits for each performance variable. Several subjects received additional training to bring their performance within tolerance limits. During the second session, a placebo injection was administered to familiarize subjects with the injection procedure. The first atropine sulfate injection was given during the third session, at which time the appropriate treatment sequence was initiated.

Table 1

Typical Experimental Session

TIME	ACTIVITY
1300 - 1320	Medical Check-In
1320 - 1340	1st Simulator "Flight" Baseline Data
1340 - 1400	Medical Check, Physiological Baseline Recording, Symptoms Questionnaire, and the Atropine Sulfate Injection
1400 - 1420	2nd Simulator "Flight"
1420 - 1440	Medical Check, Physiological Recording, and Symptoms Questionnaire
1440 - 1500	3rd Simulator "Flight"
1500 - 1520	Medical Check, Physiological Recording, and Symptoms Questionnaire
1520 - 1540	4th Simulator "Flight"
1540 - 1600	Medical Check, Physiological Recording, and Symptoms Questionnaire
1600 - 1620	5th Simulator "Flight"
1620 - 1640	Medical Check, Physiological Recording, and Symptoms Questionnaire
1640 - 1700	6th Simulator "Flight"
1700 -	Medical Check, Physiological Recording, Symptoms Questionnaire and Medical Surveillance
	TOTALS = 2 hours in Flight Simulator
	4-hour Experimental Session

An RN with advanced cardio-pulmonary resuscitation training (ACLS) administered the atropine sulfate using an intramuscular injection in the upper outer quadrant of the hip. The injections were alternated each experimental session between the right and left hips.

All drugs were administered according to actual weight. The injections used normal saline with bacteriostat to yield constant volumes for each subject, and the actual volume depended upon the subject's weight compared with the 75 kg standard. Using the treatment order shown in Table 2, the subjects received atropine injections of 0, 0.006, 0.013, 0.026, and 0.053 mg/kg, which corresponded, respectively, to the 0, 0.5, 1.0, 2.0, and 4.0 mg/75 kg treatment conditions.

The first flight for each experimental session served as a baseline flight. The appropriate injection of atropine sulfate was administered during the rest period following the first flight after baseline physiological data had been collected. Performance data on the primary and secondary tasks were collected for the remaining five flights. ECG and respiration rate were recorded during the rest periods following the remaining five flights. All data were collected under double blind conditions.

Experimental Design

Four levels of atropine sulfate and a placebo were administered to each of the 20 subjects over the course of five experimental sessions. A five by five Latin Square design was used to balance drug order effects and each subject received each of the four levels of atropine and placebo (Table 2). Each row had four subjects who were randomly assigned; therefore, there were four subjects per group and each group had a different treatment schedule.

The flight performance and Sternberg task data were automatically recorded onto eight-inch magnetic diskettes for each experimental session. Following each experimental session, the raw data files were summarized and stored on diskettes for subsequent analysis.

For the primary task dependent variables, either one or two bytes of information was used to code the flight performance data. For the turn coordinator instrument, one byte was used and two bytes each were used for information from the altimeter, localizer, and glideslope instruments. The decimal equivalent of the unsigned binary (DEB) number for either 8 or 16 bits of information represented full scale deflection for the various instruments. The RMS values were recorded and analyzed in DEB units. The scaling factors to convert from DEB to actual units are listed in Appendix A. The distributions of the RMS variables were transformed using a natural logarithm transformation to normalize the distributions.

Table 2

Latin Square for Atropine Sulfate Treatments[a]

	Experimental Session				
	1	2	3	4	5
Group[b]					
1	0.5	1.0	2.0	0	4.0
2	0	0.5	1.0	4.0	2.0
3	4.0	0	0.5	2.0	1.0
4	2.0	4.0	0	1.0	0.5
5	1.0	2.0	4.0	0.5	0

Note. The treatments are expressed in mg/75 kg.

[a]Replicated for each flight.

[b]Four subjects per group.

The results of the five experimental sessions were compiled into a master summary file and transferred to a mainframe computer for statistical analysis using the Statistical Analysis System (SAS) package (35). The SAS procedures used included: standardizing variables, univariate plots, general linear models (GLM), analysis of variance (ANOVA), multivariate analysis of variance (MANOVA), and probit analysis. The Latin Square within subjects, repeated measures analysis (Plan 12 described by Winer (36)) was used for the ANOVA and MANOVA procedures. This plan assumes that treatment, experimental session, and flight are fixed effects and that subjects within the groups is a random variable. Residual (1), the MS for subjects (within groups) x treatment, was used as the error term to test for significance for (A) treatment, (B) experimental session, and (AB)′ Latin Square error. Residual (2), the MS for subjects (within groups) x flight interaction, was used as the error term to test for the flight (C) main effect and flight x groups interaction. Residual (3) was used to test the AC and the BC interaction, and (AB)′C. The error terms were not pooled for any of the statistical analyses.

Primary Task. The primary task consisted of a direct entry to a holding pattern, the execution of three holding patterns, and a simulated Instrument Landing System (ILS) approach for landing on runway 31 at the University of Illinois-Willard Airport. These maneuvers were performed during a 20-minute simulator flight. The primary task is illustrated in Figure 6.

The primary task was flown in a no wind condition with a low level of randomly generated vertical turbulence. The flight task started at an altitude of 3000 ft (914 m) with slow cruising power, landing gear up, and flaps half extended.

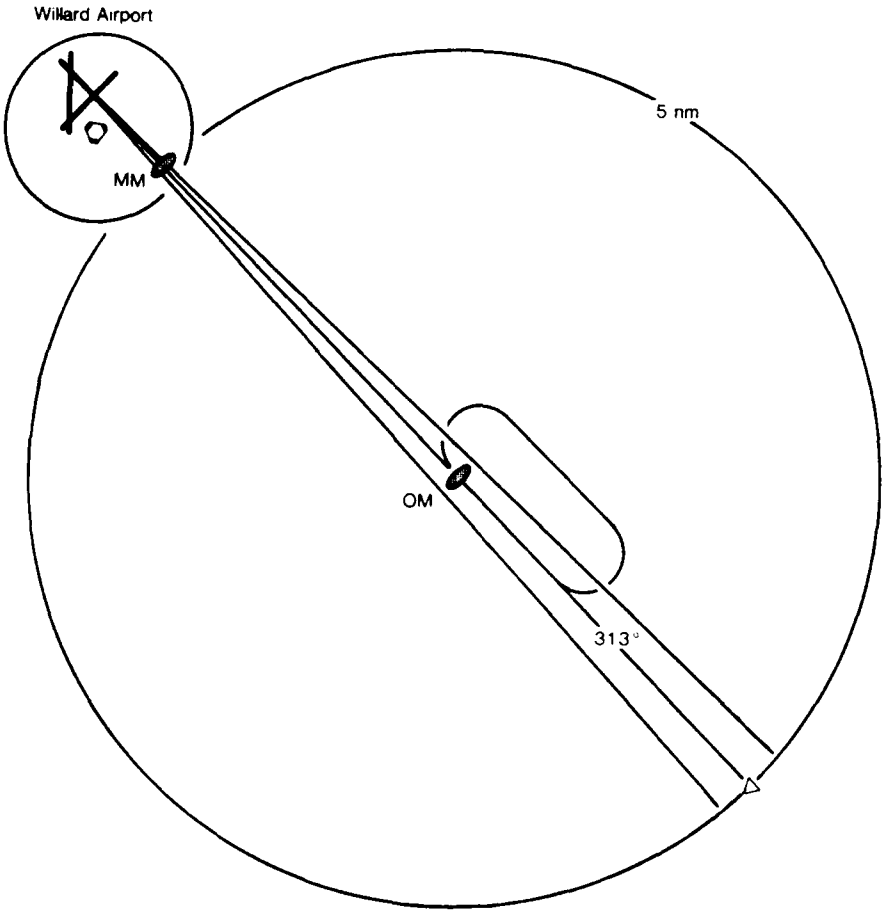


Figure 6. Primary flight task recording sheet.

The flight began five miles from the outer marker (OM) (point in Figure 6) on a magnetic bearing of 313 degrees to the ILS navigational aid located at the airport. The bearing of 313 degrees represented the extended centerline of runway 31. The outer marker was a low-frequency radio station; a visual alert was provided on the simulator instrument panel when the aircraft passed directly over the OM. The subject was instructed to track the 313 degree bearing to the outer marker, execute three holding patterns and complete an ILS approach. The standard holding pattern was oval and consisted of executing a 180 degree standard rate turn (20 degrees of bank, at 3 degrees of turn per second), tracking an outbound heading of 133 degrees for one minute, completing a second 180 degree standard rate turn, and tracking an inbound bearing of 313 degrees for one minute. The holding pattern was initiated and completed at the outer marker.

Prior to completion of the third holding pattern, the computer automatically generated verbal instructions that the subject was cleared for the ILS approach. The ILS approach from the OM to the runway consisted of a two-dimensional tracking task involving indicators that operate independently. For this task, the subjects used a standard ILS approach instrument, as shown in Figure 7 (the top, center instrument). The vertical indicator, the localizer of the ILS instrument, represented the extended runway centerline bearing of 313 degrees and provided lateral tracking information. The deflection limits of the localizer indicator were +/- 1.5 degrees. The horizontal indicator, the glideslope of the ILS instrument, represented a 3 degree angle of descent to the runway and provided vertical tracking information. The deflection limits of the glideslope indicator were +/- 0.7 degrees. The difficulty of the tracking task increased as the runway was approached. The subject was instructed to keep both tracking needles centered by establishing the appropriate descent rate and simultaneously turning the aircraft to track the localizer. The glideslope trajectory is illustrated in Figure 8. The approach terminated with a simulated landing on runway 31.

Throughout the primary task, the flight parameters of altitude, rate of turn, localizer, and glideslope tracking were automatically sampled at 1 Hz by the computer. The flight variables were stored in separate arrays during both the holding and approach phases, depending on whether or not a Sternberg task was being presented. The differences between these arrays were used to test for Sternberg task intrusion on the primary task. During the holding phase, the flight variables were also stored in separate arrays depending upon whether the aircraft was turning or in straight and level flight. This distinction was made because the flight task was considered to be more difficult during the turning portions.

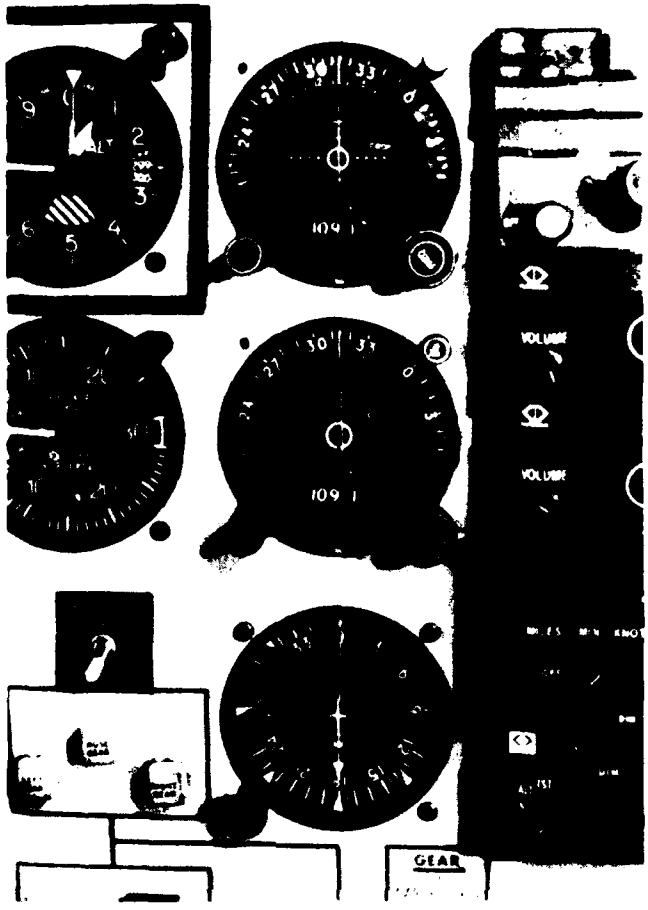


Figure 7. Navigational indicators on the ILLIMAC flight panel (TOP - Instrument Landing System (ILS) indicator, CENTER - VHF Omni Range (VOR) indicator, and BOTTOM - Automatic Direction Finding (ADF) indicator).

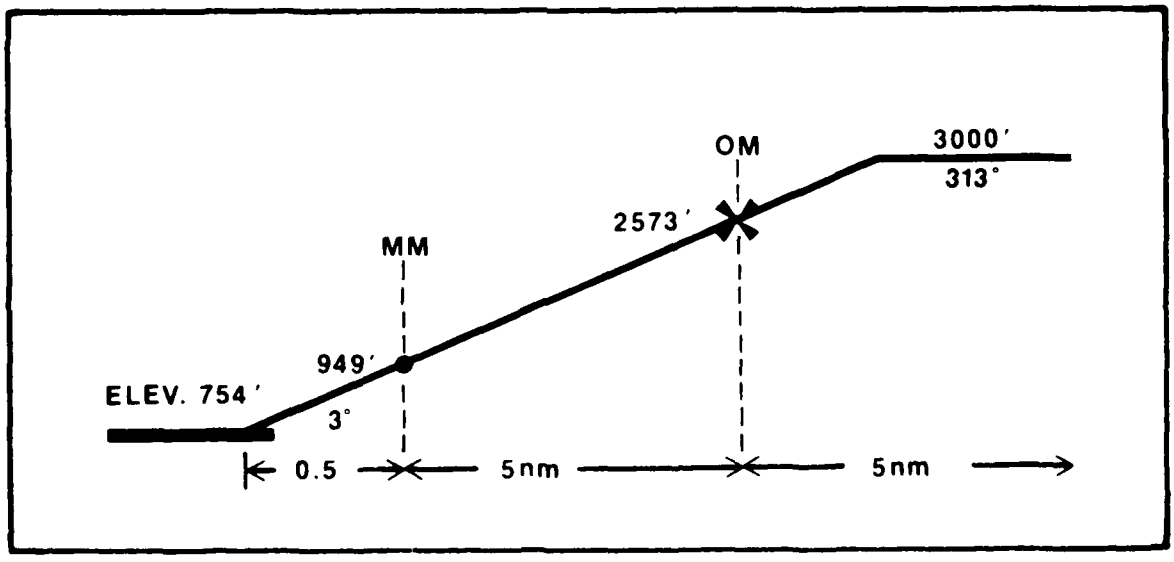


Figure 8. Profile view of the primary flight task glide path.

Secondary Task. During the flight, the Sternberg choice reaction time task was randomly presented as a secondary task to increase the workload of the subject. The secondary task consisted of the presentation of a warning signal, followed a second later by a positive set of either 2 or 4 letters that was randomly generated for each presentation from a pool of 18 letters. Presentation of the positive set sizes of 2 or 4 letters was alternated. The letters were presented by a voice synthesizer. The test probe letter was presented four seconds after the last positive set letter, and the probe had a 50% probability of being a member of the set. The four-second delay was incorporated to allow the echoic short-term auditory store to fade (22). The subject was instructed to respond by pressing a thumbswitch on the control wheel forward if the probe was a member of the positive set (true) and pulling aft if it was not (false) (25). The subject was instructed to move the left thumb to the switch upon hearing the warning tone. Reaction time was recorded with a resolution of 33 msec, and if a response was not given within three seconds, then an error was recorded. The presentation of the secondary task required ten seconds. The secondary task was programmed to occur randomly at a 50 percent probability (i.e., 60 times out of 120 possible ten-second intervals during a twenty-minute flight).

Prior to each simulator flight, the subjects were instructed to "Aviate, Navigate, and Communicate." This instruction provided the following priorities: first, control the aircraft; second, practice appropriate instrument procedures; and third, respond to the secondary communication task.

Physiological Recording. The physiological recordings were made in a private room with the subject resting comfortably in a chair with feet raised. Five minutes of ECG and respiration data were recorded onto stereo magnetic tape during the rest period following each simulator flight. ECG leads were attached to the right wrist, the left ankle, and the left arm. The thoracic belt was fastened securely around the lower ribs to monitor expansion during normal breathing.

After the physiological recording session, subjects answered a 13-item symptoms checklist (Appendix B). They were instructed to indicate how they felt at the time and how they normally felt. The symptoms were directed at specific anticholinergic effects (i.e., dryness of the mouth, tachycardia, cycloplegia, photophobia, dry hot skin, difficulty swallowing, and palpitations). Other symptoms were added and not expected to yield consistent responses (i.e., nausea, headache, ringing ears, fatigue, hyperactivity, and difficulty talking).

RESULTS

Primary Task

Simulator flight data for heading, airspeed, relative bearing, rate of turn, and lateral and vertical tracking were sampled once per second. Six root mean square (RMS) deviation values were computed (see Table 3).

Table 3

Primary Task Dependent Variables

Flight Phase	Dependent Variable
	Root Mean Square (RMS) Errors
Holding	Altitude Error While Straight and Level (ALT1)
Holding	Altitude Error While Turning (ALT2)[a]
Holding	Turning Rate Control While Straight and Level (TC1)
Holding	Turning Rate Control While Turning (TC2)[a]
Approach	Localizer (Lateral) Tracking Error (LOC)
Approach	Glideslope (Vertical) Tracking Error (GS)

[a] Rate of Turn > 1.5 degrees per sec.

Samples were collected from the start of the primary task until initiating the ILS approach to compute the RMS values for altitude and turning rate. The localizer and glideslope RMS tracking errors were computed for the ILS approach segment. Equation 1 was used to compute the RMS values.

$$RMS = \text{Square Root} \frac{SUM\ (X_i - X_t)^2}{N} \quad (1)$$

Where: RMS = Root Mean Square
X = Sample Parameter (Altitude, Banking, Localizer, or Glideslope)
X_i = Value for the i Sample of Parameter X
X_t = Target Value for Parameter X
N = Total Number of Samples

The mean RMS errors were plotted as a function of time (flight) for each of the six primary task dependent variables for the five treatment conditions. (See Figures 9, 10, 11, 12, 13, and 14). The predominant treatment effect can be seen by following the time course of the 4.0 mg/75 kg treatment condition. For all dependent variables, the increased mean RMS error for the 4.0 mg treatment condition is apparent for the second post-injection flight (time 1:00). The error continues to increase or to remain essentially the same throughout the remainder of the experimental session for the 4.0 mg conditions for all dependent variables. No increased RMS error can be seen for the first post-injection flight (time :20) for any treatment condition. There appears to be no difference between the control and the 0.5 and the 1.0 mg treatments. The 2.0 mg treatment condition shows increased RMS error for the fourth (time 2:20) and/or fifth (time 3:00) post-injection flight for ALT1, ALT2, TC1, LOC, GS.

The log RMS scores for the twenty subjects during the last five flights (post-injection) were used in a multivariate analysis of variance to test the main effects of treatment (atropine sulfate dose level), experimental session (column), flight, group (row), and subjects (nested within groups). The data for one subject for one flight was missing. The Latin Square within subjects, repeated measures analysis previously described was used for the MANOVA (36). An approximate F-Test, based on Wilks' Criterion (37) resulted in $F(24, 193) = 2.60$, $p<.0002$ for the treatment main effect.

An approximate F-test, based on Wilks' criterion, was used to test the main effect of flight (time since injection); the results were $F(24, 193) = 2.83$, $p<.0001$. The main effect of subjects nested within groups was significant, $F(90, 1592) = 29.32$, $p<.0001$. The main effects of experimental session and group were not significant. The treatment x flight interaction was significant, $F(96, 1604) = 1.53$, $p<.0009$. The treatment by period, group by flight, and period by flight interactions were not significant.

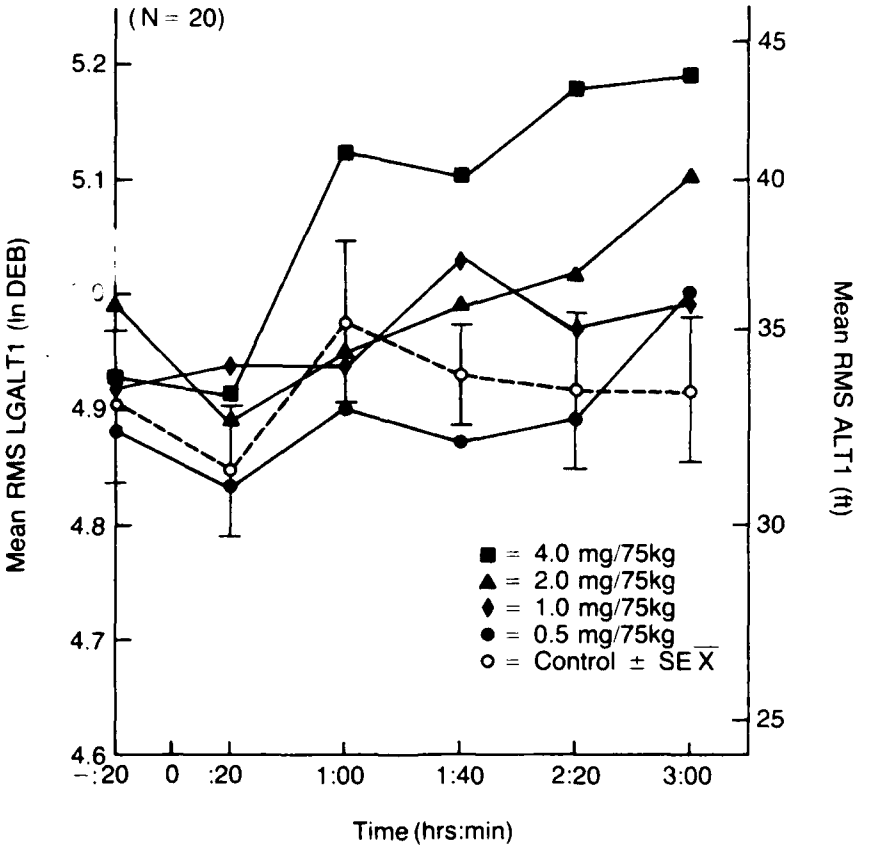


Figure 9. Mean root mean square (RMS) error for ALT1 (straight and level altitude control) versus time for five treatment conditions.

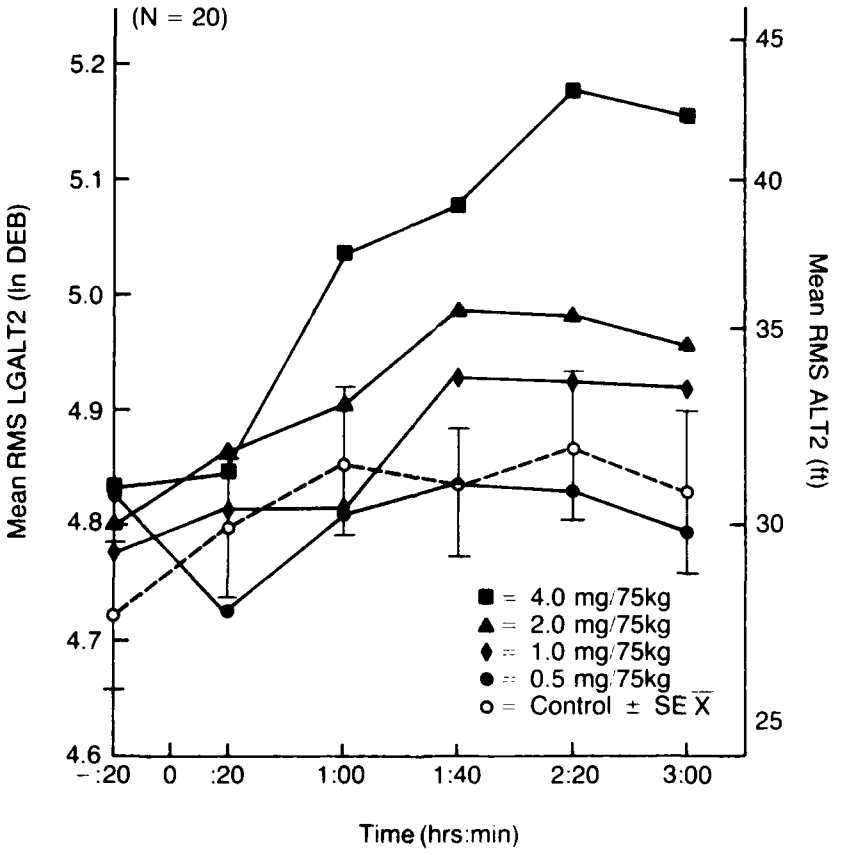


Figure 10. Mean root mean square (RMS) error for ALT2 (altitude control while turning) versus time for five treatment conditions.

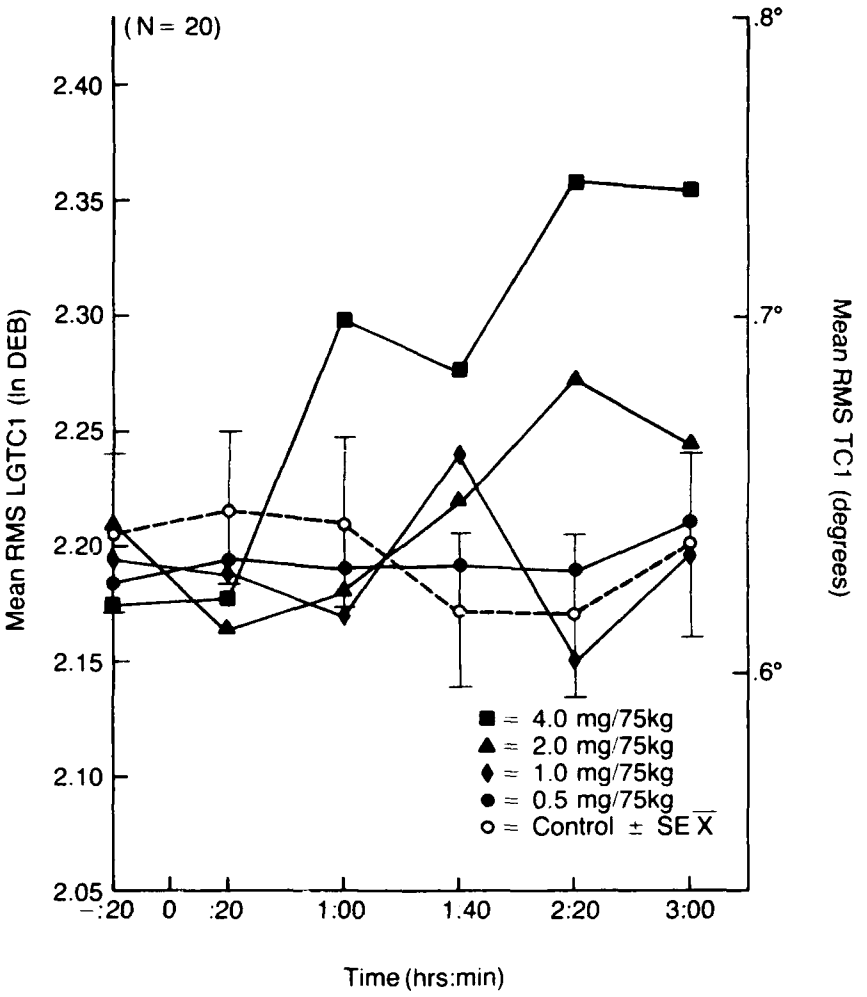


Figure 11. Mean root mean square (RMS) error for TC1 (straight and level turning rate control) versus time for five treatment conditions.

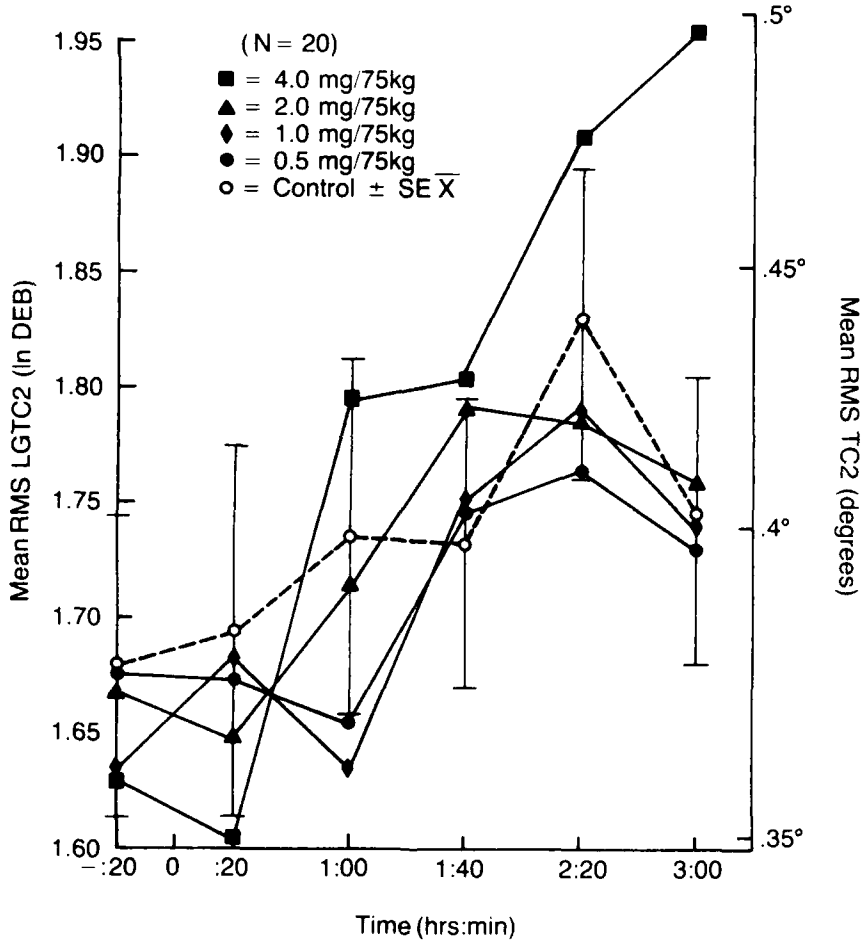


Figure 12. Mean root mean square (RMS) error for TC2 (turning rate control while turning) versus time for five treatment conditions.

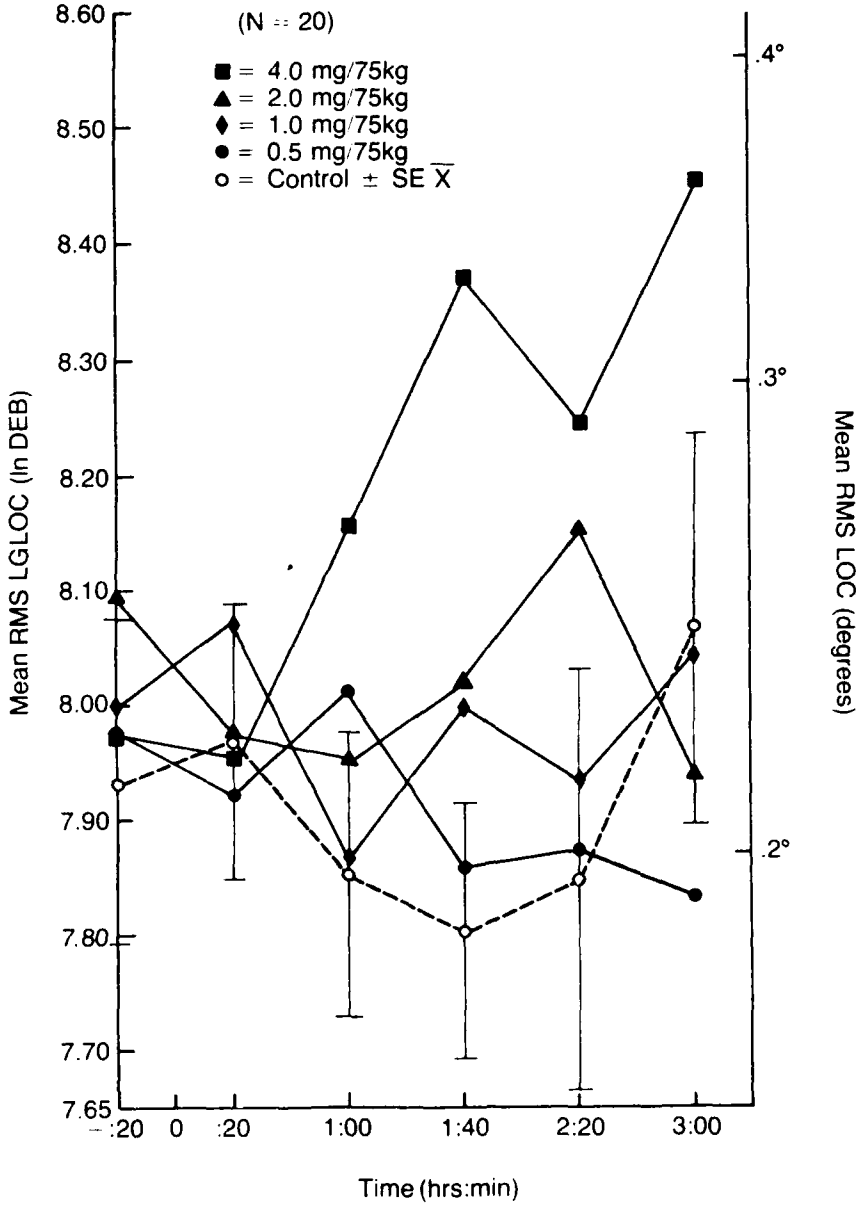


Figure 13. Mean root mean square (RMS) error for LOC (horizontal or localizer tracking) versus time for five treatment conditions.

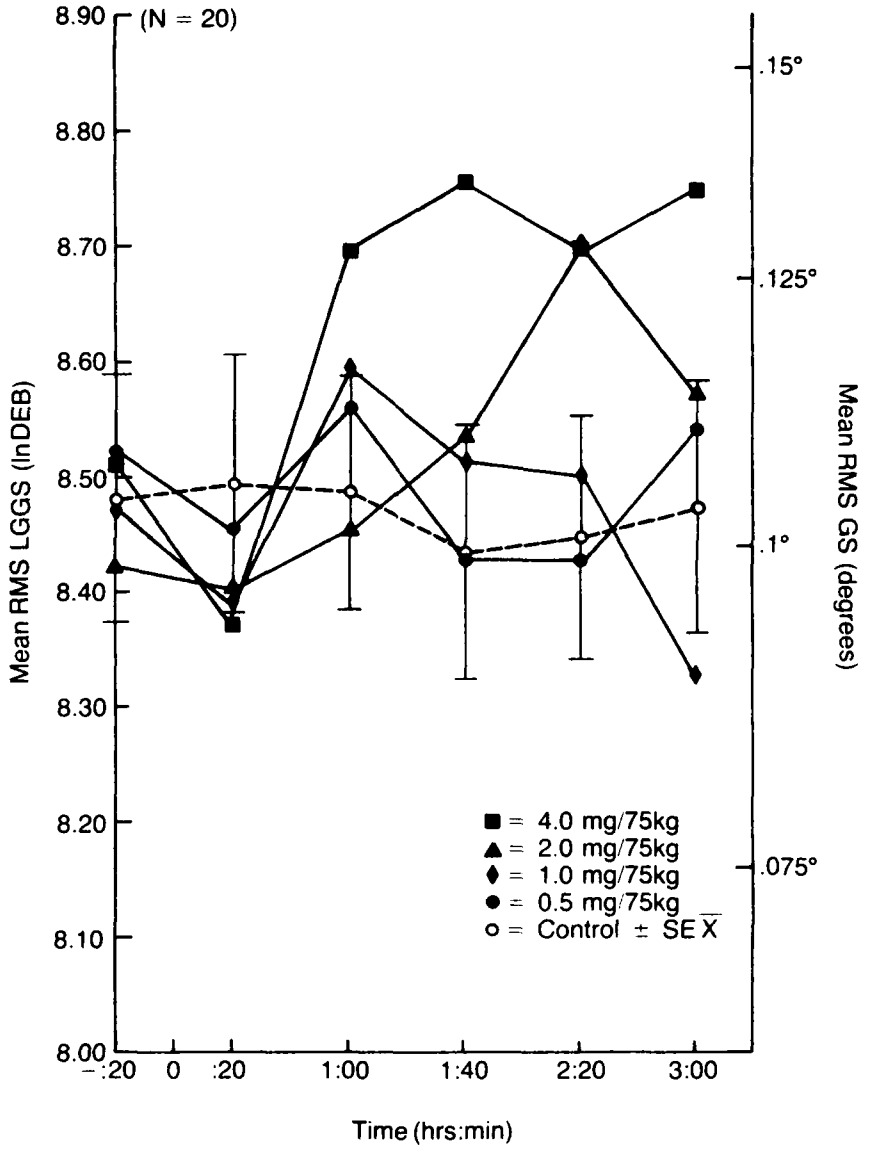


Figure 14. Mean root mean square (RMS) error for GS (vertical or glideslope tracking) versus time for five treatment conditions.

The main and interaction effects for each of the six primary task dependent variables were tested using analyses of variance (36). Table 4 summarizes the results of the six ANOVAS. All six analyses had significant treatment effects. Linear contrasts between the control and each of the four treatment levels of atropine indicated that the treatment effect was primarily due to the difference between the control and the 4.0 mg treatment level. The 0-4 mg contrasts for all six dependent variables were significant; the ALT1, ALT2, TC1, and LOC contrast had a $p<.001$ level of significance; the GS contrast had a significance level of $p<.01$; and the TC2 contrast had a $p<.05$ level of significance. The contrast between the control and the 2.0 mg treatment level for ALT2 (altitude control while turning) was significant, $p<.05$. The main effect of flight was significant for five of the primary task dependent variables (LOC was the only exception). The treatment by time since injection interaction (treatment x flight) was significant for four primary task dependent variables: TC1, TC2, LOC, and GS. The experimental session effect was significant for TC2 only. Therefore, TC2 was plotted by experimental session to illustrate the trend (Figure 15). Turning rate control while turning (TC2) was significantly improved during the course of the experiment.

In order to determine the time during which atropine produced the most significant decrement in pilot performance, MANOVAs were computed for each flight using the model previously discussed (36). The treatment main effect was significant for flights 3, 4, 5, and 6, but not for flight 1 (pre-injection) and flight 2 (the first post-injection flight). The F-values and associated probabilities for the treatment effects for flights 3, 4, 5, and 6 are as follows: flight 3, $F(24, 193) = 1.87$, $p<.01$; flight 4, $F(24, 189) = 1.88$, $p<.01$; flight 5, $F(24, 193) = 2.30$, $p<.001$; flight 6, $F(24, 193) = 2.92$, $p<.0001$.

ANOVAs were computed for each of the six primary task dependent variables for each flight. The results are summarized in Table 5. The results indicate no significant differences for any of the dependent variables for flights 1 and 2. Significant differences were found for three of the primary task dependent variables, ALT1, ALT2, and TC1 for flights 3, 4, 5, and 6, and for LOC for flights 4, 5, and 6. A significant difference was found for GS for the sixth flight and significant differences were found for TC2 for flights 3 and 6.

Table 4

Summary of the F-Statistics for the Six Analyses of Variance for the Primary Flight Dependent Variables

ANOVA Effect	Dependent Variable Tested					
	ALT1	ALT2	TC1	TC2	LOC	GS
Treatment[a]	8.10***	10.98***	9.49***	2.79*	7.90***	3.16*
Flight[a]	6.43***	5.60***	5.16***	11.53***	1.24	2.62*
Subject[b]	41.40***	38.15***	62.74***	44.02***	33.55***	37.96***
Group[a]	0.95	1.27	0.42	0.87	2.51	0.46
Session[a]	0.89	0.29	0.22	2.62*	0.73	0.88
Treatment x Flight[c]	1.50	1.30	3.89***	1.71*	2.31**	1.81*

Note. The F-Statistics are reported for all main effects and those interactions which were significant for any of the primary task variables. The variable names for the abbreviations are listed in Table 3.

*$p<.05$. **$p<.01$. ***$p<.001$.

[a]$F(4, 60)$. [b]$F(15, 359)$. [c]$F(16, 359)$.

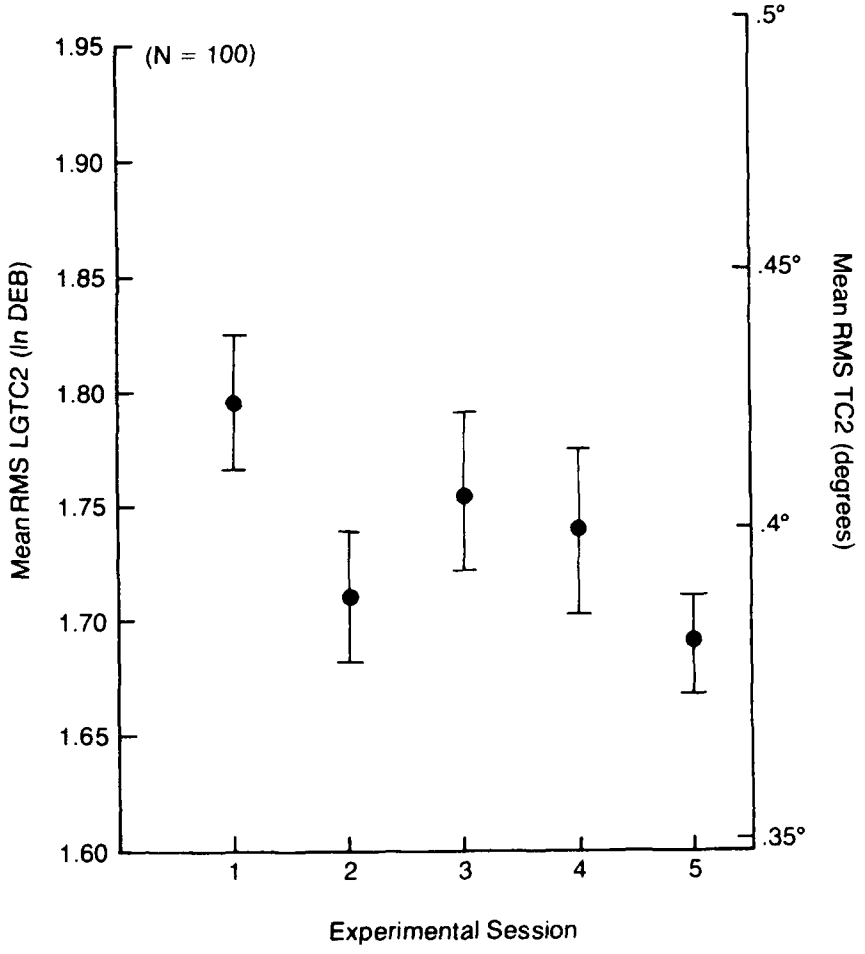


Figure 15. Mean root mean square (RMS) error for TC2 (turning rate control while turning) versus experimental session.

Table 5

Summary of the F-Statistics for the Treatment Effect for the Six Primary Task Dependent Variables for Each Flight

Primary Task Dependent Variable	Flight[a]					
	1	2	3	4	5	6
ALT1	NS	NS	3.43**	4.39**	6.91***	3.31*
ALT2	NS	NS	3.45**	4.81**	6.41***	6.54***
TC1	NS	NS	5.19***	3.54**	13.06***	8.54***
TC2	NS	NS	3.85**	NS	NS	4.04**
GS	NS	NS	NS	NS	NS	4.22**
LOC	NS	NS	NS	6.84***	3.36*	7.42***

*$p<.05$. **$p<.01$. ***$p<.001$.

[a] $F(4, 60)$.

Contrasts were computed between the control and each of the other treatment conditions. The results of the contrasts are shown in Table 6. The primary loci of the performance decrements are in the 0 versus 4.0 contrasts.

The log RMS scores for the six primary task dependent variables for the fifth flight (2:20 post-injection) were converted to standardized scores. Standardized scores for each treatment condition were plotted on one graph (Figure 16). The standardized RMS values for five of the six primary task dependent variables (ALT1, ALT2, TC1, LOC, and GS) showed a monotonic increase from the 0.5 to the 4.0 mg treatment level. Turning rate control while turning (TC2) was greater than the control only at the 4.0 mg treatment level. Three of the six variables (ALT1, ALT2, and GS) had improved performance at the 0.5 mg dose compared to the placebo control.

Table 6

Summary of Linear Contrasts for Treatment Effect for Six Primary Task Dependent Variables for Each Flight

Primary Task Dependent Variable	Contrasts					
	1	2	3	4	5	6
ALT1	NS	NS	0-4*	0-4**	0-4***	0-2* 0-4***
ALT2	NS	NS	0-4**	0-2* 0-4***	0-4***	0-4***
TC1	NS	NS	0-4**	0-4***	0-2*** 0-4***	0-4***
TC2	NS	NS	0-1*	NS	NS	0-4**
GS	NS	NS	NS	NS	NS	0-4**
LOC	NS	NS	NS	0-4***	0-2* 0-4**	0-4**

*$p<.05$. **$p<.01$. ***$p<.001$. NS = Not Significant.

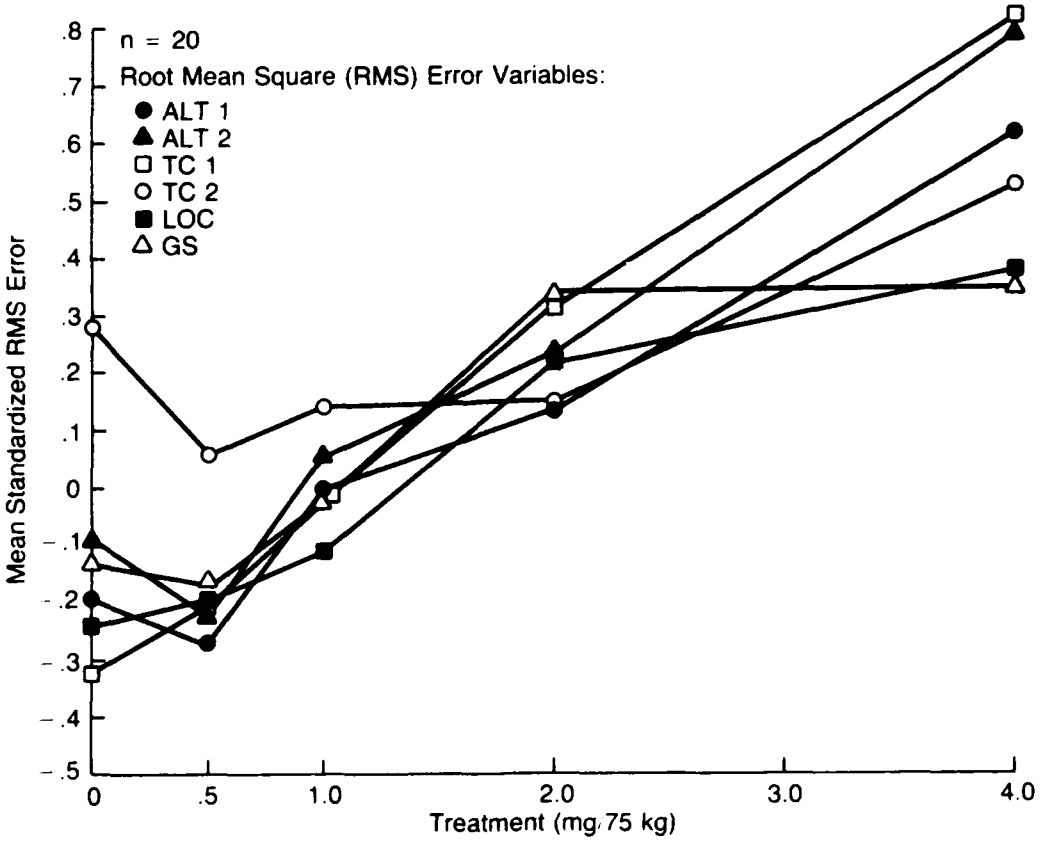


Figure 16. Standardized root mean square (RMS) tracking performance versus atropine sulfate treatment at 2:20 post-injection.

Procedural and Fatal Errors. The flight path recorder tracings of lateral tracking for the holding and approach phases of the simulator flight task were visually inspected. Figure 17 illustrates typical performance for the control (placebo) treatment condition that represents "acceptable" performance. Three flight instructors visually scored the 600 data sheets for "procedural" and "fatal" errors. Procedural errors were defined as evidence of deviation from normal FAA instrument flight procedures, temporary loss of directional control or navigational signals, minor deviations outside of protected airspace, or improper holding pattern timing. These errors were considered significant, but were not expected to lead to damage to persons or property had they occurred during normal aircraft operations. Fatal errors were errors that resulted in major deviations outside of protected airspace, procedural errors from which there was no recovery, or other errors which were likely to cause injury to persons or property damage.

The reliability of the inter-rater judgments between each of the three instructors was determined. Correlation coefficients were calculated by comparing the number of subjects with procedural and with fatal errors at each treatment level (summed for the last five flights). Procedural and fatal errors were summarized separately. Ten pairs of scores were used to compute each correlation coefficient. The reliability coefficients were .953, .943, and .937, which indicated that, when summarized in this manner, the flight instructors' judgments were similar. In order to determine the inter-rater reliability of the judgments of procedural and fatal errors at the individual flight level, a separate count was made of the number of procedural and the number of fatal errors by each experimenter for each flight. The basic data set consisted of 600 pairs of judgments for procedural and for fatal errors for each pair of raters. Three correlations were computed for the procedural errors and three for the fatal errors. The correlation coefficients for the procedural errors were .56, .60, and .67; and for the fatal errors the coefficients were 50, .57, and .74. Due to the lack of inter-rater reliability at the individual flight level, the data were not analyzed further.

Sternberg Secondary Task

In order to test for intrusiveness of the Sternberg task on the primary task, the differences between each of the following primary task dependent variables with the Sternberg on versus off were computed and used as the raw data for a univariate ANOVA test: ALT1, ALT2, TC1, TC2, LOC, and GS. Only TC2 had a significant main effect (Session, $F(4, 60) = 2.49$, $p=.04$). Two variables, TC2 and ALT2 had significant interactive effects. These were the flight x group interaction for ALT2 ($F(16, 60) = 2.03$, $p=.03$) and the flight x subject (group) interaction for TC2 ($F(60, 358) = 1.49$, $p=.01$). The overall intrusiveness of the Sternberg task on the primary task was minimal. More importantly, these findings suggest that whatever

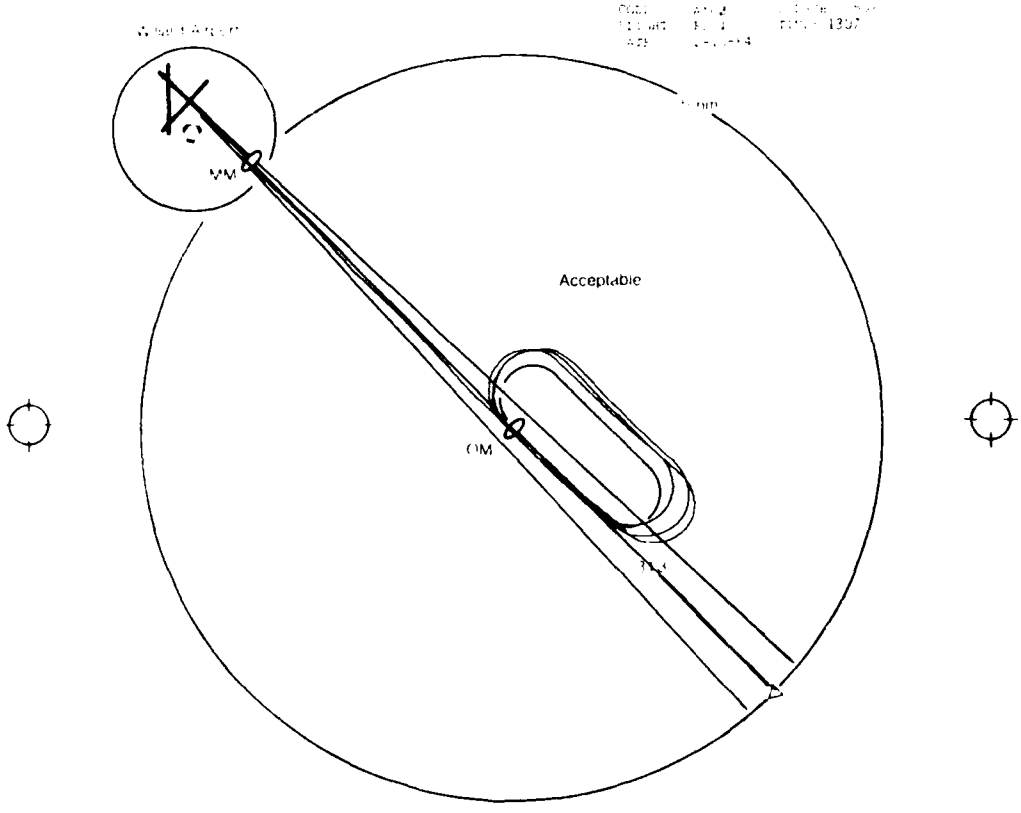


Figure 17. Sample flight path recording for an "acceptable" flight (subject = AT60, pre-injection flight, and session = 2).

effect the Sternberg task may have had on flight performance, it did not differ between drug treatment levels.

In order to determine if the subjects traded speed for accuracy in their response to the Sternberg task across treatment sessions, the percent accuracy and reaction times in seconds were plotted for the holding and the approach phases of flight for each treatment level and for the 2 and 4 positive set size. The accuracy and reaction time data for the true and false responses are cross plotted in Figure 18. Compared to the approach phase, higher accuracy and faster response times were found for the holding phase for both positive set sizes, 2 and 4. The data for the two phases lie in completely non-overlapping clusters. The results clearly show the decreased level of performance and the increased variability for both accuracy and reaction time during the approach phase. The data indicate that the Sternberg task was a good secondary task. As the difficulty of the primary task increased during approach, the speed of responding on the Sternberg task sharply decreased and the accuracy of responding also decreased substantially. The random pattern of data for the 2 and 4 positive set size and across the different treatment levels within the approach and the holding phases clearly indicates that there were no speed-accuracy trade-offs as a function of treatment level.

To examine the effect of drug dose level on performance of the Sternberg task itself, the mean true and false reaction times for the five post-injection flights for the twenty subjects were plotted as a function of positive set size (2 and 4) for each of the treatment levels. The reaction times for the holding phase and the approach phase were graphed separately (Figure 19).

The data plotted in Figure 19 fail to reveal any apparent consistent treatment effects during either the holding or approach phases for the true and false reaction times. In addition, the variability during the approach phase was substantially greater than during the holding phase. As a consequence of this variability, a decision was made to focus the primary analysis on the Sternberg data from the holding phase. During the holding phase, the slopes for the true reaction times were positive and the true reaction times were faster than the false reaction times. These results are consistent with the Sternberg model. The negative slopes of the false reaction times for the holding phase, however, are not consistent with the Sternberg model.

An analysis of variance was used to test the significance of the main effects of treatment, flight, session, group, positive set size, and true-false for the reaction time dependent variable; the following first order interactions were also tested: treatment x true-false; treatment x positive set size; and the positive set size x true-false interactions for the reaction time dependent variable. There was no or period main effects significant. The true-false main effect was

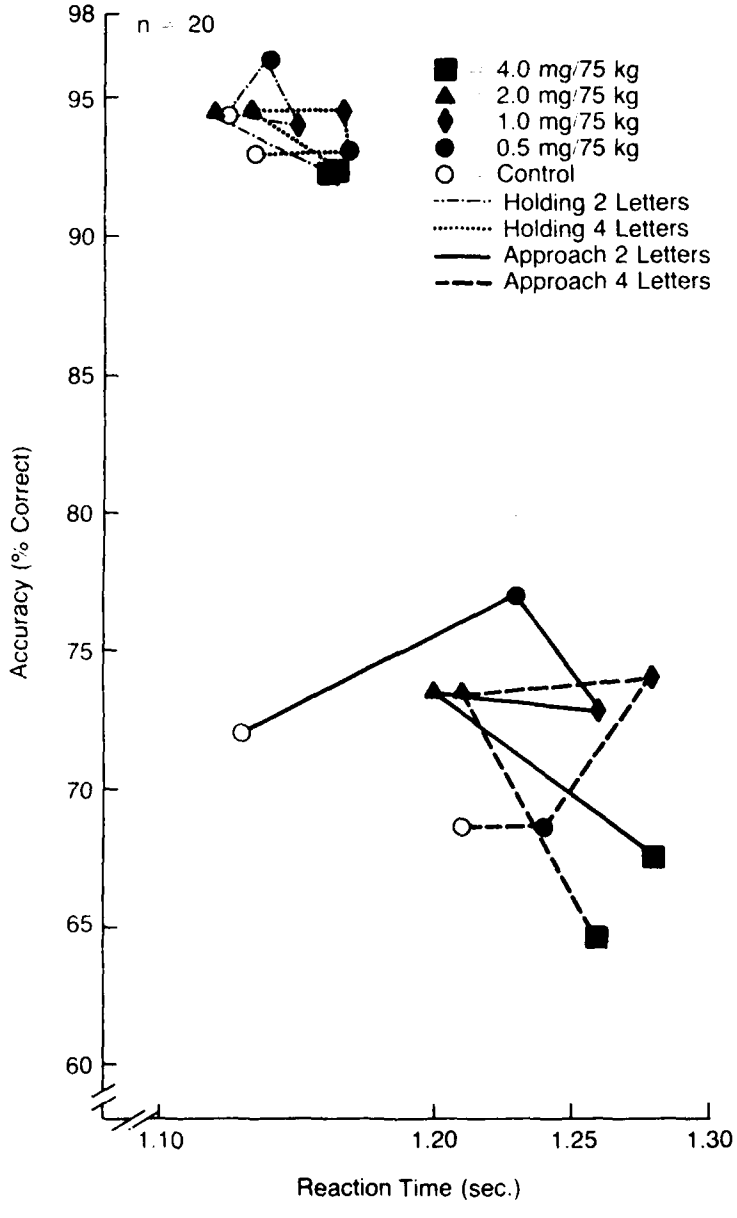


Figure 18. Percent accuracy (ACC) versus reaction time (RT) by treatment and flight phases.

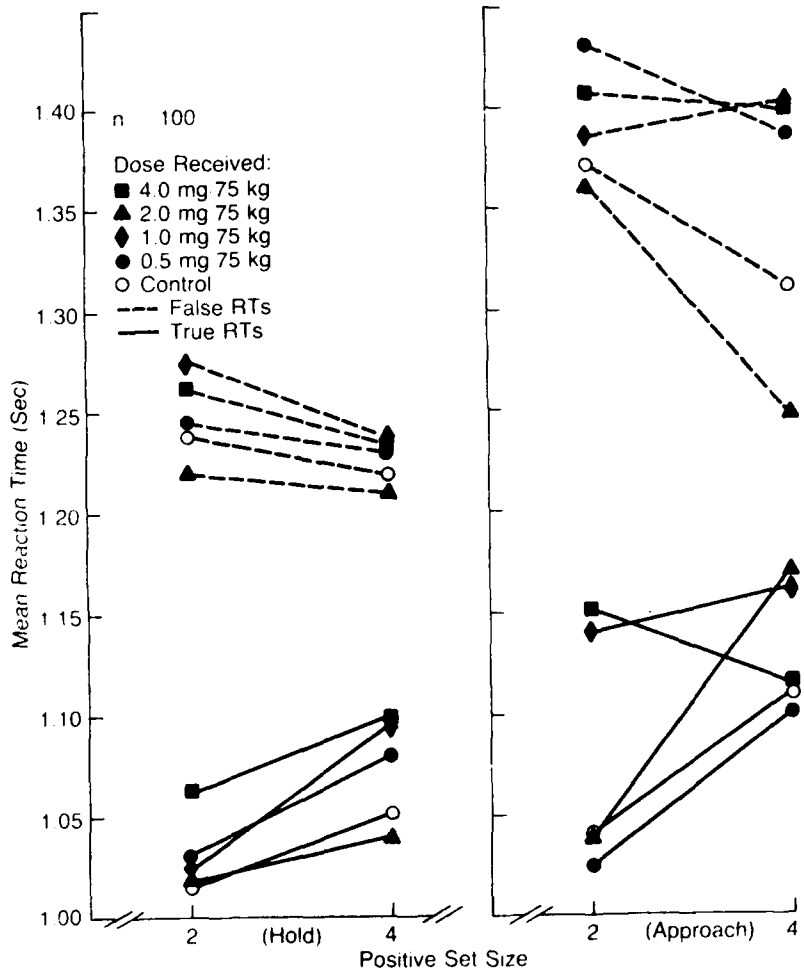


Figure 19. Mean Sternberg reaction time (RT) for the five post-injection flights by positive set size, flight phase, response type, and treatment received.

treatment main effect, nor were the flight, positive set size, group significant, $F(1, 15) = 69.1$, $p<.0001$. The true-false x positive set size interaction was significant, $F(1, 15) = 9.95$, $p<.007$, as was the treatment x period interaction $F(16, 76) = 4.16$, $p<.0001$.

An ANOVA was used to test the significance of the main effects of treatment flight, session, group, and positive set size for the accuracy dependent variable; first order interactions were also tested. There was no treatment main effect, nor were the flight, group, session, or positive set size main effects significant. The treatment x session and the treatment x positive set size were significant ($p<.01$).

Physiological Results

The ECG and respiration recordings were analyzed using the spectral analysis methods described by Porges et al. (26). The ECG data collected during each five-minute recording period were digitized and the mean heart period and the heart period variance were computed. The digitized data were analyzed to compute $\hat{V}$, or the variance of the heart period for the frequency band which corresponds with normal respiration (i.e., 0.12 to 0.40 Hz). The $\hat{V}$ and the HPV were transformed using a natural logarithm transformation to normalize the distributions. The respiratory recordings were submitted to spectral analysis to verify that breathing frequencies remained in the 0.12 to 0.40 Hz frequency band.

Means for the MHP, the HPV and the $\hat{V}$ distributions were computed for each treatment condition for each of the six physiological recording periods. These means are illustrated in Figures 20, 21, and 22, respectively. The -:05 time period for each figure represents the pre-injection baseline recording for each of the five treatment conditions. The mean and the standard error of the mean (SE X) for the control treatment condition for each time period are shown in each figure as well as the means for the four levels of atropine. The pre-injection baseline data for all three dependent variables are closely grouped, which indicates no pretreatment differences.

The means for the heart period data (Figure 20) reveal several important trends. There is a decrease in MHP for the 4.0, 2.0, and 1.0 mg treatment conditions for the first post-injection time period (:35). The peak effect for the 4.0 mg treatment condition occurred during this period and was followed by a gradual recovery which was still in progress at the end of the experimental session. The time course of the 2.0 mg treatment condition was similar, but the gradual recovery was not seen until the third post-injection period (1:55). The peak effect of the 1.0 mg treatment condition occurred during the second post-injection period (1:15) followed by a gradual recovery which was complete by the fifth post-injection period (3:15). The 0.5 mg treatment condition showed an increase in the mean heart period

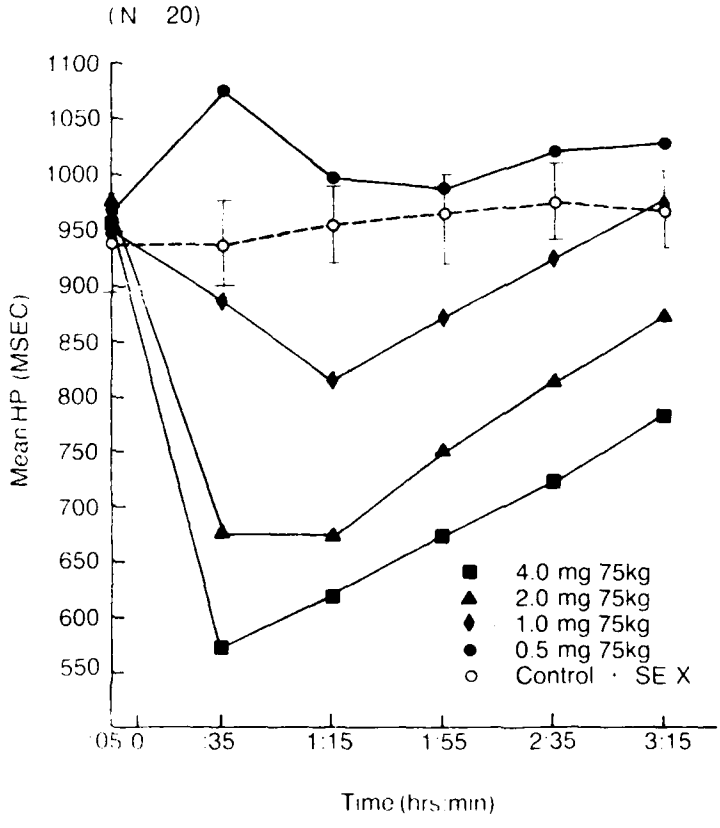


Figure 20. Mean heart period (MHP) versus time for five treatment conditions.

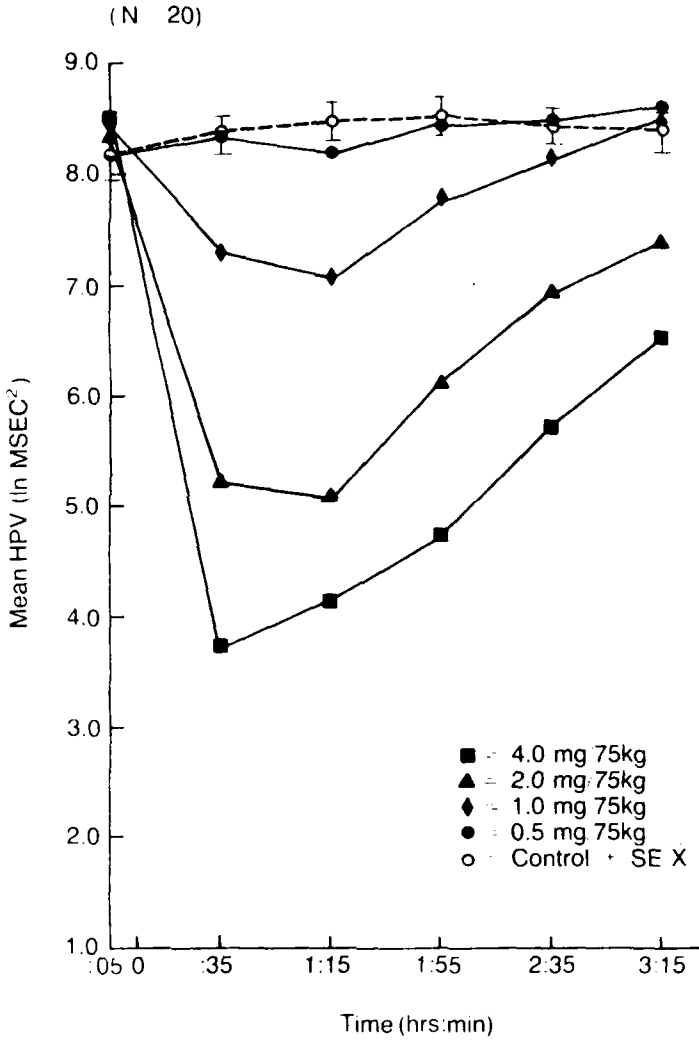


Figure 21. Mean heart period variance (HPV) versus time for five treatment conditions.

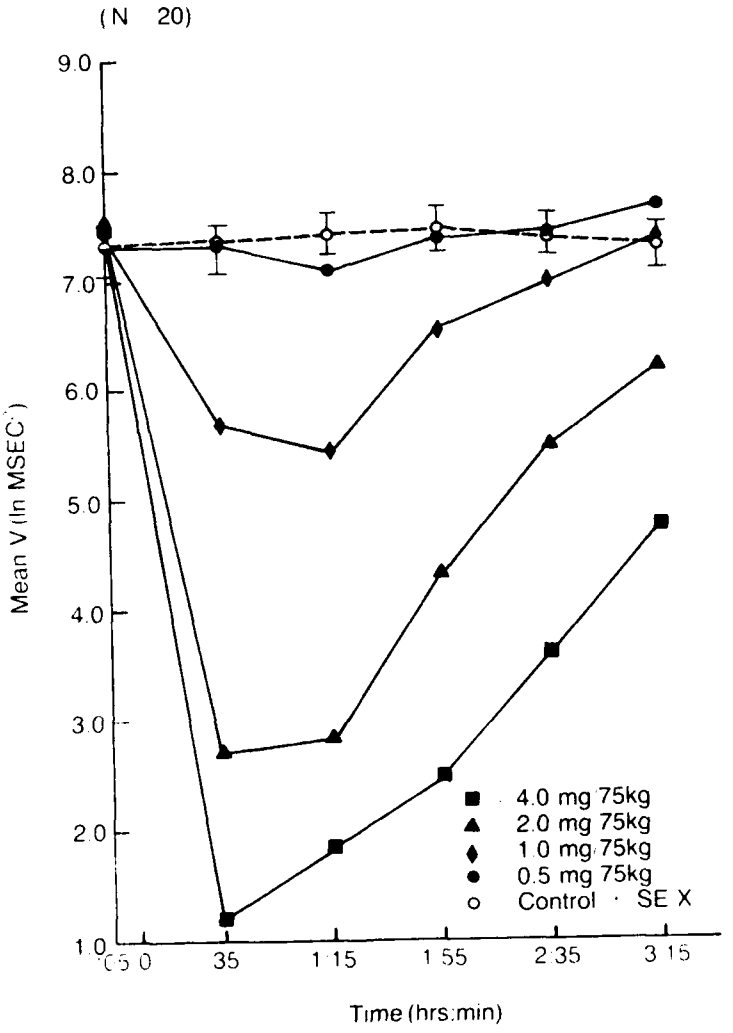


Figure 22. Mean respiratory sinus arrhythmia amplitude estimate ($\hat{V}$) versus time for five treatment conditions.

followed by a recovery. The mean for three of the final four post-injection periods for the 0.5 mg treatment condition slightly exceeded +1 SE X.

Examination of the HPV means (Figure 21) and the $\hat{V}$ means (Figure 22) indicates similar dose-response time trends for the 4.0, 2.0, and 1.0 mg treatment conditions as those observed for the MPH treatment. The means for the 0.5 mg treatment condition, however, do not appear to deviate significantly from the control mean for any of the post-injection time periods for either the HPV or the $\hat{V}$ treatment condition.

The pre-injection recording (time = -:05) was tested for significance. The pre-injection main effect for group (dose sequence and randomly assigned subjects to groups) was not significant for any of the three dependent variables.

ANOVAs for the MHP, HPV, and $\hat{V}$ dependent variables, using the Latin Square within subjects, repeated measures analysis (36) were used to test the significance of the main effects of treatment, time (post-injection time period), subjects (nested within groups), group (row), and experimental session (column) for each of the three dependent variables. The first order interaction effects were also tested. The results for the main effects and the treatment x time interaction of the three ANOVAs for MHP, HPV, and $\hat{V}$ are summarized in Table 7.

For all three dependent variables, the main effects of treatment and time (post-injection) were significant as was the treatment by time interaction. The subjects (nested within groups) effect was also significant, but the group and experimental session main effects were not significant. The significant treatment by time (post-injection) interaction described the time duration of the atropine sulfate effect. In order to examine the time course of the treatment effect of atropine, an analysis of variance was computed for each post-injection time period for each dependent variable. The treatment main effect for each post-injection time interval was significant for each of the three dependent variables. The F-statistics for all tests were significant ($p<.0001$).

Linear contrasts were used to determine treatment effects between the placebo and each of the other four treatment conditions. The results of the linear contrasts for each of the post-injection times for the three dependent variables are summarized in Table 8.

The contrasts between the control and the 2.0 mg and between the control and the 4.0 mg treatment conditions for all three dependent variables were significant ($p<.0001$) for all post-injection time periods, which indicates that the MHP, HPV, and $\hat{V}$ all failed to return to the control level during the experimental session. The contrasts

Table 7

Summary of the F-Statistics for the Three Analyses of Variance for the Physiological Dependent Variables

Main and Interaction Effects	Dependent Variable		
	MHP	HPV	$\hat{V}$
Treatment[a]	102.09*	206.48*	70.93*
Time[a]	102.17*	152.97*	11.17*
Subjects[b] (Nested within Groups)	312.09*	51.18*	7.32*
Group[a]	0.75	0.36	0.20
Session[a]	1.37	0.60	1.15
Treatment x Time[c]	30.59*	23.87*	3.46*

*$p<0.001$.

[a]$F(4, 60)$. [b]$F(15, 284)$. [c]$F(16, 284)$.

Table 8

Summary of the Linear Contrasts for Treatment Effect for Physiological Dependent Variables for Each Post-Injection Time Period

	Time Post-Injection				
Treatment Contrast (mg/75 kg)	:35	1:15	1:55	2:35	3:15
Mean Heart Period (MHP)					
0 - 0.5	****	NS	NS	NS	*
0 - 1.0	NS	****	****	*	NS
0 - 2.0	****	****	****	****	****
0 - 4.0	****	****	****	****	****
Heart Period Variance (HPV)					
0 - 0.5	NS	NS	NS	NS	NS
0 - 1.0	****	****	***	NS	NS
0 - 2.0	****	****	****	****	****
0 - 4.0	****	****	****	****	****
Respiratory Sinus Arrhythmia Amplitude ($\hat{V}$)					
0 - 0.5	NS	NS	NS	NS	NS
0 - 1.0	NS	****	***	*	NS
0 - 2.0	***	****	****	****	****
0 - 4.0	****	****	****	****	****

*$p<.05$. **$p<.01$. ***$p<.001$. ****$p<.0001$.

NS = Not Signficant.

between the 0 and the 1.0 mg treatment condition were significant for the first three post-injection periods for the HPV; these contrasts were significant for the second (1:15), third (1:55), and fourth (2:35) post-injection periods for the MHP and $\hat{V}$. The contrasts between 0 and 1.0 mg were not significant for the final post-injection period (3:15) for any of the three dependent variables. This finding indicates that the recovery was complete for all three dependent variables at 3:15 post-injection for the 1.0 mg treatment condition. None of the contrasts were significant between the 0 and 0.5 mg treatment conditions for HPV and $\hat{V}$ and only the first contrast for the :35 post-injection period and the last (3:15) for MHP was significant. Examination of Figure 20 clearly indicates that the first difference was the result of a significant increase in the MHP (bradycardia) for the 0.5 mg treatment condition for the first post-injection period compared to the control condition. The 0.5 mg treatment condition had no significant effect on HPV or $\hat{V}$.

The respiratory data were subjected to spectral analysis and the resultant spectral densities were checked to verify that the dominant respiratory frequency occurred within the 0.12 to 0.40 Hz range for all subjects during all treatments. Six hundred analyses were examined; 97% displayed a maximal respiratory peak within the specified range (see the example in Figure 23a). Approximately 10% (of the 97%) had some interference from cardiac activity at the high frequencies. However, in the analyses with cardiac interference, the normal respiratory peak was still observable (Figure 23b). Less than 2% displayed peak respiratory frequencies greater than or equal to the limits of the 0.12 to 0.40 Hz range, and 1% of the recordings were unreadable. Therefore, the use of the normal respiratory range was justified for the RSA estimates in the present study.

The ED50s of the atropine for the three dependent variables were estimated using probit analysis. The quantal response used as the criterion was a 30% decrease in MHP, HPV, or $\hat{V}$. The number of individuals that had a 30% decrease for each treatment level was used for the probit analysis for each dependent variable. The ED50s of atropine for the 30% decrease were:

(a) MHP = 2.52 mg ($\chi^2(2, \underline{N}=4) = 2.57, \underline{p}=.28$);

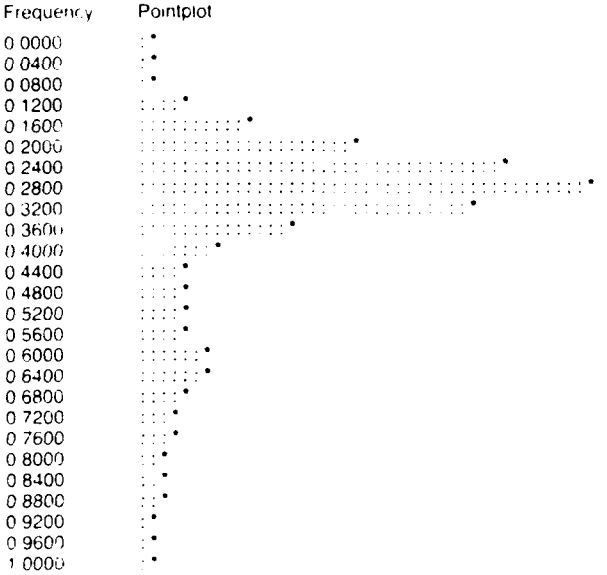
(b) HPV = 1.61 mg ($\chi^2(2, \underline{N}=4) = 6.58, \underline{p}=.04$); and

(c) $\hat{V}$ = 0.98 mb ($\chi^2(2, \underline{N}=4) = 1.21, \underline{p}=.55$).

When the ED50s of the three dependent variables were compared, RSA amplitude ($\hat{V}$) was the most sensitive indicator of the vagolytic effects of atropine sulfate.

A

Power Spectra for Respiration



B

Power Spectra for Respiration

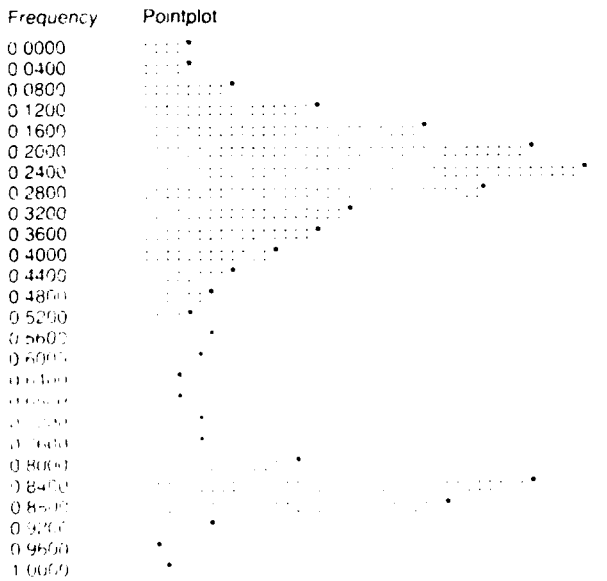


Figure 23a & 23b. Power spectra pointplots for sample respiration data: (a) normal respiration (0.12 to 0.40 Hz), (b) cardiac interference on respiratory plot at 0.84 Hz.

The baseline (pre-injection) and control (zero dose) estimates of RSA were examined using the average range (AR) metric of Sidell and Kaminskis (38). The highest AR observed for an individual was 38.5% and the mean AR over all 20 subjects was 15.0%.

Symptoms Checklists. The number of individuals who reported symptoms on the checklists was tallied for each treatment level and ED50s were estimated for 6 of the 13 symptoms using probit analysis. These six symptoms were the most frequently and consistently reported symptoms during the study. The other seven were either poorly correlated to dose, or the estimates obtained were unrealistic. The results for the six symptoms are listed in Table 9. The ED50 estimate for the symptom, "Dry Mouth," was 0.34 mg of atropine and the Chi-Square of 1.34 indicated a good fit of the estimated probit line. The ED50 of 2.11 mg of atropine for "Difficult to Swallow" on the Chi-Square of 0.06 indicated that the data fit the probit line estimate. For the symptom, "Hard to Read Checklist," the ED50 estimate was 3.29

Table 9

ED50 Estimates for Six of the Reported Symptoms

Symptom Reported	ED50 (mg)	Chi-Square[a]
Dry Mouth	0.34	1.34*
Difficult to Swallow	2.11	0.06*
Racing Heart	2.58	2.74
Hard to Read Checklist	3.29	0.90*
Lights Bright	4.28	4.38
Fluttery Chest	5.07	0.35*

Note. ED50 = the effective dose level (mg) at which 50% of the individuals display the response (symptom).

*$p > .10$.

[a] $^2(1, N = 4)$.

mg of atropine with a Chi-Square of 0.90, which indicated a good fit. Finally, the ED50 for "Fluttery Chest" was 5.07 mg of atropine; the Chi-Square of 0.35 indicated a good fit to the estimated probit line. Good fits to the probit line estimate were not obtained for "Racing Heart", with an estimated ED50 of 2.58 mg of atropine and for "Lights Bright," with an estimated ED50 of 4.28 mg of atropine.

Post-Participation Questionnaire. After the study ended, the subjects were asked to complete the post-participation questionnaire in Appendix C. Nineteen of the twenty subjects complied. From those results, it is apparent that all persons receiving 4.0 mg of atropine sulfate perceived the effects. About two-thirds complained of visual problems, and approximately one-third complained of dizziness, headache, fatigue, and confusion. Eleven (59%) reported that the symptoms were worse than expected and would not participate in a similar experiment again. The side effects of the 4.0 mg treatment level were felt for an average of 14 hours with a range of 2 to 48 hours reported.

DISCUSSION

The results from the primary task dependent measures clearly indicate the effects of atropine on pilot performance. Each of the six primary task dependent measures were significantly affected by atropine and all variables except the localizer tracking variable showed a significant time (flight) effect. The time x flight interaction was significant for four of the primary task dependent variables. None of the primary task performance decrement effects, however, were observed for the first post-injection simulator flight. The first significant effects were found for the second post-injection flight (1:00 post-injection). Contrasts for this flight indicated that the effects were due to the differences between the 0-4 mg treatment condition for altitude and heading control while straight and level, and for altitude control while turning. These variables were the most sensitive of the primary flight dependent measures to the effects of atropine. Significant effects were found for this treatment level for the remainder of the flights at the following post-injection time periods: 1:40, 2:20, and 3:00.

The final flight occurred 3 hours post-injection and was the only flight for which the treatment effects for all of the primary flight dependent measures were significant. Contrasts for this flight indicated that the principal treatment effect was the 4.0 mg dose level, although one 0-2 mg contrast was significant. These data and the mean RMS error data for all six primary task dependent variables for the 4.0 mg treatment level fail to indicate any substantial trend toward reversal of the performance decrement process. Indeed, a substantially longer experimental session would have been required to permit performance to return to the baseline condition.

The contrasts for the treatment effect for the six primary task dependent variables for each flight indicated that the 0-4 mg treatment contrast was significant for 17 of 18 contrasts computed. This finding indicates that the 4.0 mg treatment condition produced the most significant effects for each dependent variable across the last four post-injection time periods. Four of the cells which had significant 0-4 mg contrasts also had significant 0-2 mg contrasts, which indicated that the 2.0 mg treatment level produced a substantial performance decrement. The 0-1 mg contrast for the TC2 variable for the third flight was significant.

The 4.0 mg treatment condition consistently resulted in performance decrements for flight tasks observed. Some performance decrements occurred for the 2.0 mg treatment level, but these decrements appeared later, were not as consistent across flight tasks, and generally persisted for a shorter time duration compared with the 4.0 mg treatment effects. These dose-response relationships were expected. No substantial primary task performance decrements should be expected for the 0.5 and the 1.0 mg treatment conditions.

A comparison of the six primary task dependent variables at the 2:20 post-injection time period indicated that five of the variables showed a monotonic increase in mean RMS error (reduced performance) as the level of atropine was increased beyond 0.5 mg. This finding demonstrated the orderliness of the dose-response of atropine when measured by the primary task dependent measures. Other investigators have found dependent variables involved in a pilot's control of a flight simulator to be sensitive to the following toxic substances: secobarbitol (7); alcohol, (8, 9, 10, 11, 12); marijuana, (13); and anti-emetic drugs, (14). The present study has clearly demonstrated that RMS error for altitude and heading control while both straight and level and turning, and for dual task tracking is effective in detecting over time the dose-response effects of atropine.

Some performance decrement should be expected within 1:40 after injecting 2.0 mg of atropine and substantial performance decrements should be expected within 1:00 hour of administering a 4.0 mg injection of atropine. The substantial performance effects of the 4.0 mg dose level should be expected to continue for over two hours.

Klein (39) recommended that the known performance decrements resulting from ethanol be used as references for other drugs. In order to provide this reference, the average decrements from this study were compared to the results of a study (12) which used methods similar to those used in the present study to examine the effects of 0.014%, 0.038%, and 0.082% Blood Alcohol Levels (BALs). The difference between treatment means and the placebo means for the five primary tasks, for which a significant alcohol treatment effect was found, was used to calculate the percentage performance decrement for the 0.082% BAL level for the five dependent variables. The percentage

performance decrements ranged from 4.4% to 11.1%. These decrements for the 0.082% BAL level were used as the quantal response criteria. The number of subjects for each atropine treatment level that exceeded the criteria for any of the five dependent variables was calculated. Probit analysis was used to estimate the ED50 for the level of atropine equivalent to the decrement found for the 0.082% BAL ethanol level. The result was an ED50 of 3.12 mg of atropine sulfate ($^2(1, N=4) = 0.0001$, $p= .997$). The Chi-Square provided a very good fit to the probit line estimate. These data indicate that in fifty percent of the pilots, the performance decrement on at least one of the primary flight tasks caused by a 3 mg injection of atropine will be similar to that caused by a 0.082 BAL.

It should be noted, however, that this analysis was provided in order to give some indication of the magnitude of the performance decrement as a result of a 2.0 or 4.0 mg atropine injection. There is some evidence that the observed performance decrements on the primary tasks may represent a conservative estimate of pilot performance that may occur in the aircraft. Billings et al. (7) found smaller performance decrements in the simulator than in the aircraft.

The Sternberg task clearly fulfilled its role as a secondary task, loading the pilot's residual capacity. This load was most clearly demonstrated by the differences in Sternberg task performance between holding and approach phases.

Interestingly, despite the pronounced effects of drug treatment on the primary flight task, drug treatment failed to show any influences on the Sternberg task. Three possible explanations may be offered for this lack of effect:

(1) Subjects treated the Sternberg task as "primary," and allocated resources away from the flight task to protect it from the detrimental effects of the drugs. This appears to be unlikely, however, because, as reported above, the effect of the Sternberg task on tracking performance did not differ as a function of drug level. It would have been expected to do so, if the subjects had treated the Sternberg task as a primary task.

(2) Systematic drug effects on the Sternberg task were masked by the high degree of between and within subject variability in the measure. This variability, coupled with the low power of the design, led to the negative effects that were observed. This explanation is also somewhat unlikely because the data in the holding phase were in fact quite orderly with regard to the effects of set size and response type. This orderliness would not have been expected had there been high levels of variability.

(3) The third hypothesis is that atropine sulfate failed to influence the cognitive processes involved in performing the Sternberg

task. This conclusion then requires an examination of the differences between the Sternberg task (unaffected) and the flight task (affected). Task analysis reveals a large number of characteristics upon which the two tasks differ. These include the complexity and modality of the input (one auditory input versus several visual inputs), the code of central processing (verbal versus spatial), and the complexity of response (discrete versus analog). It can be stated with some degree of certainty that it is not simply the greater absolute difficulty of the flight task that led to its greater susceptibility to the treatment. Such an explanation might account for a difference in effect between single task flight and single task Sternberg performance, but not between single task flight and dual task Sternberg. In fact, if the absolute difficulty were responsible for the difference in effect, then the greatest drug effect should be expected in the dual task condition. This, of course, was not found. Determining precisely which information processing characteristics made the Sternberg task immune from the atropine sulfate levels employed here, while at the same time caused flight performance to be adversely affected, will require that further data be collected in order to examine information processing skills.

Aside from the absence of a drug effect on the Sternberg task, a secondary effect that was of interest was the significant interaction between memory set size and response type. The unexpected form of this interaction related to the negative slope of the false responses (i.e., "false" responses were faster to a set size 4 than to a set size 2). While Sternberg's memory search model provides no ready accounting for such a finding, the assumptions of that model are based entirely on single task data. In contrast, Micallizi and Wickens (20) reviewed the applications of the Sternberg Task to dual task environments and noted two investigations, by Spicuzza, Pincus, and O'Donnel (40) and Crawford, Pearson, and Hoffman (41), in which negative slopes in the Sternberg Task were obtained in dual task conditions. Interestingly, both of these studies involved applications of the Sternberg task to the flight simulator environment with auditory stimulus presentation--precisely the same conditions employed here. Furthermore, the negative slope for "false" responses obtained in the present results is also consistent with the data from a second study currently being conducted in our laboratory.

Research is currently underway in our laboratory to determine the possible cause of the negative slope for "false" responses. One specific hypothesis is that, when confronted with a stimulus that does not match a representation in memory on a set size 4 trial, subjects truncate their search process. The consequence would be a more rapid, but potentially less accurate response (i.e., an increased chance of saying "no" to a positive stimulus). This strategy in turn would produce a higher error rate for positive stimuli. The data from the ongoing study are currently being examined to determine if this is the case.

At the present time we are unable to interpret the treatment x experimental interaction found for both the RT and accuracy variables. The treatment x set size is also puzzling. Further studies will be required to interpret these interactions.

The MHP, HPV and $\hat{V}$ data clearly indicate the physiological effects of atropine sulfate and the time course of the effect. The decrease in MHP for the 4.0, 2.0, and 1.0 mg treatment conditions observed during the first post-injection recording period (:35) was expected. Other investigators (3, 4, 5) have reported an early onset of rapid tachycardia. Since the peak effect of reduced MHP for the 4.0 mg treatment was observed during the first physiological recording period in the present study, the early time course and the absolute peak effect cannot be determined with certainty. The gradual recovery of MHP for the 4.0 mg treatment condition was orderly and still in progress at the end of the experimental session. The time courses of the 2.0 mg and the 1.0 mg treatment conditions were similar to the time course of the 4.0 mg treatment condition. The observed dose-response relationships were also expected. The MHP data for the 0.5 mg treatment level showed the expected bradycardia followed by a recovery. Cullumbine et al. (3) reported similar increases in mean heart period for low atropine levels.

The HPV and the $\hat{V}$ means showed similar dose-response time trends as those observed for the MHP means, except no bradycardia was observed for the 0.5 mg treatment condition. Higher atropine levels resulted in rapid parasympathetic effects as had been reported by Ketchum et al. (4). The rapid onset of the physiological effects and partial recovery indicates rapid blocking of the vagal influence on the heart. The observed partial recovery from the vagal block for the 2.0 and 4.0 mg dose levels during the final two hours, while performance effects were increasing, may indicate that the predominant vagal effect of atropine sulfate, at these dose levels, is related to the afferent feedback from the stretch receptors of the lungs to the medullary area. Porges et al. (26) discussed this physiological mechanism as one of the mechanisms for RSA. Yongue et al. (27) had previously demonstrated that injections of atropine methylnitrate in rats produced a peripheral block of the vagus and decreased $\hat{V}$.

As expected, the dose-response relationships for performance effects, physiological effects and symptoms varied significantly among the individual subjects. Probit analysis provided estimates that account for individual differences. Comparisons of the estimates of the atropine level at which 50% of the population will experience a 30% decrease in MHP clearly indicated that $\hat{V}$ was the most sensitive indicator of the effects of atropine on the vagal influence of the heart. These findings support the conclusions of Yongue et al. (27). They concluded that $\hat{V}$ is sensitive to changes in the vagal influence on the heart and that $\hat{V}$ responded in a different manner than MHP and HPV.

The heart period data in this study were converted to heart rate in order to compare the results to those reported by Ketchum et al. (4). The ED50 for a 30% increase in heart rate was computed after converting the heart period data to estimated heart rates (HR = 1000 / HP x 60). This ED50 was 1.66 mg ($\chi^2(2, N=4) = 2.478$, $p=.29$). The ED50 calculated to be 1.32 mg by Ketchum et al. (4) was similar to that observed in the present study. The minor difference between the estimates was probably due to the longer sample intervals (40 minutes) in the present study. The use of probit analysis to rank order subjective symptoms and to give estimates of ED50s is informative. As expected, if a 0.5 mg injection of atropine sulfate is given, one can expect 50% of the population to experience dry mouth. Clinically, 0.4 mg of atropine sulfate is used to produce that particular symptom. A 1.0 mg level of atropine will produce the same effect for a longer duration. The 2.0 mg level will produce difficulty in swallowing and some complaints of tachycardia. The 4.0 mg level will produce higher incidences of the symptoms produced by the lower dose as well as visual effects that may be very significant to aviators.

The side effects from the 4.0 mg atropine injection were reported to continue for an average of 14 hours after the injection. This finding was comparable to the typical duration of effects reported by Ketchum et al. (4) of 10 to 12 hours. The subjects' comments about dizziness and the occasional note by the RNs about ataxia indicate that these symptoms should also be quantified in future atropine sulfate studies.

The use of atropine sulfate during complex task performance is not normally recommended. However, in the case of military pilots who are required to operate in a high risk chemical warfare environment, auto-injection and/or pretreatment with atropine sulfate may be essential to survival. A single 2.0 mg atropine self-injection is expected to result in some reduced ability to perform complex pilot tasks, and should be used only when there is a very high probability of exposure. This conclusion is different than that reported by Cullumbine et al. (3), who reported that 2.0 mg can be recommended as a safe dose in the absence of anticholinesterase exposure. A 4.0 mg injection was found to produce significant performance decrements and to clearly increase the risk of error by pilots while performing complex tasks. In the case of known chemical agent exposure, the tolerance to atropine sulfate, however, is much greater and one assumes that atropine can be injected without increasing the risk of additional performance decrements.

The difference in the time course of the dose-response relationships for performance decrements, physiological response and symptoms was one of the most interesting findings of the present study. This finding also appears to provide information of potential operational significance for the use of atropine sulfate among Army aviators.

The performance decrements for the 2.0 mg atropine level were not significant until 1:40 post-injection. At the 4.0 mg level of atropine, the performance decrements were significant during 1:00 post-injection. On the other hand, the physiological effects were noted at :35 post-injection. Unlike the immediate parasympathetic effects (i.e., dry mouth and tachycardia), the performance decrements lag considerably. The time course of the performance and physiological effects found in this study are supported by the findings of Cullumbine et al. (3), Ketchum et al. (4), and Sawka et al. (5), who reported rapid tachycardia and dry mouth, and by Moylan-Jones (6) and Ketchum et al. (4), who reported the delayed onset of cognitive performance decrements.

This lag in performance decrements when compared to the physiological symptoms may permit the military pilot who injects atropine sulfate, but has not been exposed to a chemical agent, time to land safely. With higher levels of atropine, however, the lag between atropine injection and physiological performance effects is reduced. If an Army aviator injects 4.0 mg of atropine and experiences the effects of atropine (e.g., tachycardia and dry mouth), it is expected that performance decrements as a result of atropine sulfate will follow. The physiological symptoms can be used as an alerting signal to the aviator to land before a significant decrement in performance is experienced.

The results of the present study should provide additional information to Army policy-makers regarding the use of atropine sulfate in a high risk chemical warfare situation. These results should be replicated using Army aviators flying Army tactical scenarios. Based on the results of the present study, follow-on research should concentrate on the higher doses of atropine sulfate (i.e., 2.0 and 4.0 mg) and disregard the lower doses (i.e., 0.5 and 1.0 mg).

REFERENCES

1. Goldstein, A., Aronow, L., & Kalman, S. M. (1974). Principles of drug action: The basis of pharmacology (2nd ed.). New York: John Wiley.

2. Taylor, P. (1980). Anticholinesterase agents. In A. G. Gilman, L. S. Goodman, & A. Gilman (Eds.), Goodman and Gilman's the pharmacological basis of therapeutics (6th ed., pp. 100-119). New York: Macmillan.

3. Cullumbine, H., McKee, W. H. E., & Creasey, N. H. (1955). The effects of atropine sulphate upon healthy male subjects. Quarterly Journal of Experimental Physiology, 40, 309-319.

4. Ketchum, J. S., Sidell, F. R., Crowell, E. B., Jr., Aghajanian, G. K., & Hayes, A. H., Jr. (1973). Atropine, scopolamine, and ditran: Comparative pharmacology and antagonists in man. Psychopharmacologia, 28, 121-145.

5. Sawka, M. N., Levine, L., Kolka, M. A., Appleton, B. S., Joyce, B. E., & Pandolf, K. B. (1984). Effect of atropine on the exercise-heat performance of man. Fundamental and Applied Toxicology, 4, s190-s194.

6. Moylan-Jones, R. J. (1969). The effect of a large dose of atropine upon the performance of routine tasks. British Journal of Pharmacology, 37, 301-305.

7. Billings, C. E., Gerke, R. J., & Wick, R. L., Jr. (1975). Comparisons of pilot performance in simulated and actual flight. Aviation, Space, and Environmental Medicine, 46(3), 304-308.

8. Asknes, E. G. (1954). Effects of small doses of alcohol upon performance in a Link trainer. Journal of Aviation Medicine, 25, 680-688.

9. Henry, P. H., Davis, T. Q., Engelken, E. J., Triebwasser, J. H., & Lancaster, M. C. (1974). Alcohol-induced performance decrements assessed by two Link trainer tasks using experienced pilots. Aerospace Medicine, 45(10), 1180-1189.

10. Henry, P. H., Flueck, J. A., Sanford, J. F., Keiser, H. N., McNee, R. C., Walter III, W. H., Webster, K. H., Hartman, B. O., & Lancaster, M. C. (1974). Assessment of performance in a Link GAT-1 flight simulator at three alcohol dose levels. Aerospace Medicine, 45(1), 33-44.

11. Collins, W. E., & Chiles, W. D. (1980). Laboratory performance during acute alcohol intoxication and hangover. Human Factors, 22(4), 445-462.

12. Taylor, H. L., Dellinger, J. A., Schilling, R. F., & Richardson, B. C. (1983) Pilot performance measurement methodology for determining the effects of alcohol and other toxic substances. In A. T. Pope, & L. D. Haugh (Eds.), Proceedings of the Human Factors Society 27th Annual Meeting, 1, 334-338.

13. Janowsky, D. S., Meacham, M. P., Blaine, J. D., Schoor, M., & Bozzetti, L. P. (1976). Simulated flying performance after marihuana intoxication. Aviation, Space, and Environmental Medicine, 47(2), 124-128.

14. Taylor, H. L., Dellinger, J. A., Hyman, F. C., & Richardson, B. C. (1984). Anti-emetic drugs and pilot performance. Aviation, Space, and Environmental Medicine, 55(5), 398-402. (From Annual Scientific Meeting, 1984, Abstract No. 112).

15. Dellinger, J. A., & Taylor, H. T. (1985). Measuring the effects of neurotoxicants on flight simulator performance. Aviation, Space, and Environmental Medicine, 56, 254-257.

16. Kelley, C. R. (1969). The measurement of tracking proficiency. Human Factors, 11(1), 43-64.

17. Smith, P. J., and Langolf, G. D. (1981). The use of Sternberg's memory-scanning paradigm in assessing effects of chemical exposure. Human Factors, 23(6), 701-708.

18. Sternberg, S. (1975). Memory scanning: New findings and current controversies. Quarterly Journal of Experimental Psychology, 27, 1-32.

19. Osborne, D. J., & Rogers, Y. (1983). Interactions of alcohol and caffeine on human reaction time. Aviation, Space, and Environmental Medicine, 54(6), 528-534.

20. Micalizzi, J., & Wickens, C. D. (1980). The application of additive factors methodology to workload assessment in a dynamic system monitoring task (Tech. Rep. No. EPL-80-2). Urbana: University of Illinois, Engineering-Psychology Research Laboratory.

21. Micalizzi, J. (1984) The Structure of processing resource demands in monitoring automatic systems. Proceedings, Psychology in the Department of Defense, Ninth Annual Symposium, 430-434.

22. Wickens, C. D. (1984). Engineering Psychology and Human Performance. Columbus, OH: C. E. Merrill.

23. Sternberg, S. (1966). High-speed scanning in human memory. Science, 153, 652-654.

24. Ogden, G. D., Levine, J. M., & Eisner, E. J. (1979). Measurement of workload by secondary tasks. Human Factors, 21(5), 529-548.

25. Wolf, J. D. (1978). Crew workload assessment: Development of a measure of operator workload (Tech. Rep. No. AFFDL-TR-78-165). Wright-Patterson Air Force Base, OH: Air Force Flight Dynamics Laboratory, Air Force Wright Aeronautical Laboratories, Air Force Systems Command.

26. Porges, S. W., McCabe, P. M., & Yongue, B. G. (1982). Respiratory-heart rate interactions: Psychophysiological implications for pathophysiology and behavior. In J. T. Cacioppo & R. E. Petty (Eds.), Perspectives in cardiovascular psychophysiology (pp. 223-264). New York: Guilford Press.

27. Yongue, B. G., McCabe, P. M., Porges, S. W., Rivera, M., Kelley, S. L., & Ackles, P. K. (1982). The effects of pharmacological manipulations that influence vagal control of the heart on heart period, heart-period variability and respiration in rats. Psychophysiology, 19, 426-432.

28. McCabe, P. M., Yongue, B. G., Porges, S. W., & Ackles, P. K. (1984). Changes in heart period, heart period variablility, and a spectral analysis estimate of respiratory sinus arrhythmias during aortic nerve stimulation in rabbits. Psychophysiology, 21(2), 149-158.

29. Donchin, Y., Feld, J. M., Porges, S. W. (1984). The measurement of respiratory sinus arrhythmia as an indicator for the level of anesthesia. Unpublished manuscript. University of Illinois, Department of Psychology, Urbana.

30. Porges, S. W. (in press). Spontaneous oscillations in heart rate: A potential index of stress. In G. P. Moberg (Ed.), Animal stress: New directions in defining and evaluating the effects of stress. Bethesda, MD: American Physiological Society.

31. Klaassen, C. D., & Doull, J. (1980). Evaluation of Safety: Toxicologic Evaluation. In J. Doull, C. D. Klaassen, & M. O. Amdur (Eds.), Casarett and Doull's toxicology: The basic science of poisons (2nd ed., pp. 11-27). New York: Macmillan.

32. Sidell, F. R., & Pless, J. E. (1971). Ethyl alcohol: Blood levels and performance decrements after oral administration to man. Psychopharmacologia, 19, 246-261.

33. Taylor, H. L., Staples, L. A., Todd, R. E., & Harshbarger, T. L. (1984, May). The Illinois microcomputer aviation computer (ILLIMAC) simulator. Proceedings of the IEEE 1984 National Aerospace and Electronics Conference (NAECON 1984), 2, 1016-1023.

34. Federal Aviation Administration. (1976). Flight test guide: Instrument pilot airplane. (FAA Publication No. EA-AC 61-56A). Washington, DC: U.S. Government Printing Office.

35. SAS Institute Inc. (1982) SAS user's guide: Statistics, 1982 edition. Cary, NC: SAS Institute Inc.

36. Winer, B.J. (1971) Statistical Principles in Experimental Design, 2nd Ed., McGraw-Hill Company, Inc., New York, pp. 745-748.

37. Rao, C.R. (1973) Linear Statistical Inference and its Applications. Wiley, New York, 2nd Ed., p. 555.

38. Sidell, F. R., & Kaminskis, A. (1975). Temporal intrapersonal physiological variability of cholinesterase activity in human plasma and erythrocytes. Clinical Chemistry, 21(13), 1961-1963.

39. Klein, K. E. (1972). Prediction of flight safety hazards from drug induced performance decrements with alcohol as reference substance. Aerospace Medicine, 43(11), 1207-1214.

40. Spicuzza, R., Pincus, A., & O'Donnell, R.D. (1974, August) Development of performance assessment methodology for the digitla avionics information system. Dayton, Ohio: Systems Research Laboratories, Inc.

41. Crawford, B.M., Pearson, W.H., & Hoffman, M.S. (1978) Multipurpose switching and flight control workload. Proceedings of the Sixth Symposium on Psychology in the Department of Defense, 219-221.

APPENDIX A

CONVERSION SCALE FOR DEB UNITS

Parameter Recorded	Full Scale	Scale Number
Turn Needle (TC)	9.00 degrees	0.0703 x DEB
True Heading	180 degrees	0.0055 x DEB
Altimeter (ALT)	8000 feet	0.2441 x DEB
Airspeed	681.8 mph	0.0208 x DEB
Localizer (LOC)	2.5 degrees	7.63xE-5 x DEB
Glideslope (GS)	0.7 degrees	2.14xE-5 x DEB
ADF Needle	180 degrees	0.0055 x DEB

APPENDIX B

SYMPTOMS CHECKLIST

SUBJECT CODE _____

DATE _____

FLIGHT # _____

AVIATION RESEARCH LABORATORY

SYMPTOMS CHECKLIST - ATROPINE EXPERIMENT

Please complete this checklist after every flight.

Circle the most appropriate symptom level for your present condition.

Place an X through the point which you consider "normal" for you.

1.	Moist Cool Skin	1	2	3	4	5	Dry Hot Skin
2.	Easy to Read this Checklist	1	2	3	4	5	Hard to Read
3.	Speaking Fluently	1	2	3	4	5	Difficult to Talk
4.	Lights Dark	1	2	3	4	5	Lights Bright
5.	Slow Heart	1	2	3	4	5	Racing Heart
6.	Salivating Excessively	1	2	3	4	5	Dry Mouth
7.	No Headache	1	2	3	4	5	Head Hurts
8.	Lethargic	1	2	3	4	5	Hyperactive
9.	No Nausea	1	2	3	4	5	Nauseated
10.	Internally Calm	1	2	3	4	5	Fluttery Chest
11.	Dull Hearing	1	2	3	4	5	Ringing Ears
12.	Normal Swallowing	1	2	3	4	5	Difficult to Swallow
13.	Fatigued	1	2	3	4	5	Energetic

APPENDIX C

POST-PARTICIPATION QUESTIONNAIRE

1. a. Did you know which week you received the highest dose?

   b. How did you know?

   c. How long did you feel the effects of that dose?

      2 hrs 4 hrs 6 hrs 8 hrs 12 hrs 24 hrs

   d. Describe the effects you felt in descending order, strongest first.

      1.
      2.
      3.
      4.

2. Describe any feelings of mental confusion you had.

3. Did you ever feel out of control after the injections?

4. Were the effects you felt better or worse than you had imagined?

5. Would you run in another similar experiment? Would you encourage your friends to?

6. Can you think of any way to make the experiment better? safer?

7. Did you feel you had enough explanation of the effects/side effects of the drugs given?

8. Can you list any change in procedure that could make the experiment easier/better on your part?

9. Did you feel the length of the sessions was too long, too short or appropriate?

DISTRIBUTION STATEMENT

1 copy: Commander
US Army Medical Research and Development Command
ATTN: SGRD-RM1-S
Fort Detrick
Frederick, MD 21701-5012

5 copies: Commander
US Army Medical Research and Development Command
ATTN: SGRD-PLE
Fort Detrick
Frederick, MD 21701-5012

12 copies: Administrator
Defense Technical Information Center
ATTN: DTIC-DDAC
Cameron Station
Alexandria, VA 22304-6145

1 copy: Commandant
Academy of Health Sciences, US Army
ATTN: AHS-CDM
Fort Sam Houston, TX 78234-6100

1 copy: Dean, School of Medicine
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4799