



**Effects of the Chemical Defense Antidote
Atropine Sulfate on Helicopter Pilot Performance:
An In-flight Study**

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June 1991

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**United States Army Aeromedical Research Laboratory
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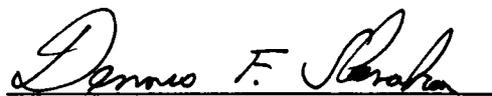
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REPORT DOCUMENTATION PAGE

Form Approved
 OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified		1b. RESTRICTIVE MARKINGS	
2a. SECURITY CLASSIFICATION AUTHORITY		3. DISTRIBUTION / AVAILABILITY OF REPORT Public release; distribution unlimited	
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE		5. MONITORING ORGANIZATION REPORT NUMBER(S)	
4. PERFORMING ORGANIZATION REPORT NUMBER(S) USAARL Report No. 91-17		7a. NAME OF MONITORING ORGANIZATION U.S. Army Aeromedical Research and Development Command	
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Aeromedical Research Laboratory	6b. OFFICE SYMBOL (if applicable) SGRD-UAB-CS	7b. ADDRESS (City, State, and ZIP Code) Fort Detrick Frederick, Maryland 21701-5012	
6c. ADDRESS (City, State, and ZIP Code) P.O. Box 577 Fort Rucker, Alabama 36362-5292		9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8a. NAME OF FUNDING / SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (if applicable)	10. SOURCE OF FUNDING NUMBERS	
8c. ADDRESS (City, State, and ZIP Code)		PROGRAM ELEMENT NO. 0603002A	PROJECT NO. 3M26300 2D995
		TASK NO. BF	WORK UNIT ACCESSION NO. 101
11. TITLE (Include Security Classification) (U) Effects of the Chemical Defense Antidote Atropine Sulfate on Helicopter Pilot Performance: An In-flight Study			
12. PERSONAL AUTHOR(S) J.A. Caldwell, Jr., D.J. Carter, R.L. Stephens, L.W. Stone, D.M. Delrie, J.Y. Pearson, and R.R. Simmons			
13a. TYPE OF REPORT	13b. TIME COVERED FROM _____ TO _____	14. DATE OF REPORT (Year, Month, Day) 1991 June	15. PAGE COUNT 195
16. SUPPLEMENTARY NOTATION			
17. COSATI CODES		18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)	
FIELD	GROUP	Atropine (sulfate), Helicopter pilots, Subjective pilot grading, Flight performance, Performance Assessment Battery (PAB), Zero Input Tracking Analyzer (ZITA), Event-related potential (ERP), Electroencephlogram (EEG), UH-1	
01	02		
05	08		
19. ABSTRACT (Continue on reverse if necessary and identify by block number) <p>The effect of 2 mg and 4 mg injections of atropine sulfate on helicopter pilots was investigated using a specially instrumented UH-1H helicopter and several laboratory tests. A counterbalanced, within-subjects design was employed in which flight performance, vision, electroencephalographic activity, cognitive skill, and tracking performance were assessed on each of three different drug administration days (placebo, 2 mg, and 4 mg) separated by control days.</p> <p>Results indicated numerous atropine-related difficulties, seen most often with the 4 mg dose. Measurements of flight performance revealed decrements on at least one measure (i.e., heading, air speed, vertical speed) in both visual- and instrument-referenced straight and level flight, standard-rate turns, a straight climb and descent, steep turns, a climbing turn, and an instrument landing system (ILS) approach. Also, there were degradations in performance of a confined area approach and an out-of-ground-effect hover maneuver. Some (continued on attachment)</p>			
20. DISTRIBUTION / AVAILABILITY OF ABSTRACT <input type="checkbox"/> UNCLASSIFIED/UNLIMITED <input checked="" type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS		21. ABSTRACT SECURITY CLASSIFICATION Unclassified	
22a. NAME OF RESPONSIBLE INDIVIDUAL Chief, Scientific Information Center		22b. TELEPHONE (Include Area Code) (205) 255-6907	22c. OFFICE SYMBOL SGRD-UAX-ST

subjects evidenced other significant in-flight problems. Vision tests showed atropine-related increases in pupil diameter and double vision, concurrent with decreases in accommodation and depth perception. Cognitive tests revealed decrements in visual search, logical reasoning, quantitative ability, short-term memory, and response times. Psychomotor tracking tasks indicated atropine-induced increases in tracking errors across three levels of tracking complexity, and these sometimes were accompanied by deficits in responding to a secondary task. Electrophysiological data revealed a number of effects on both evoked potentials and resting EEGs which were consistent with the observed atropine-related performance problems.

Overall, performance at higher altitudes under the influence of up to 4 mg of atropine did not appear to be critically impaired, but performance close to the ground which required tight control of the aircraft did reveal problems. The severity of these atropine-related decrements may increase under the "real world" scenarios of training or combat.

At this point, our results suggest when an aviator is flying at 1000 feet above ground, he's not in tight formation flight, and his aircraft is functioning properly, he is probably not in danger of crashing even under the influence of up to 4 mg atropine. However, he will suffer from slower reaction time, visual impairments, accuracy losses, and some judgment deficits, all of which will require a high degree of caution. We would recommend that once an aviator has injected atropine, he return immediately to base where he should remain grounded until the full range of atropine effects subside.

Executive summary and conclusion

The results of this investigation concerning flight performance, visual, cognitive, psychomotor, and electrophysiological effects of 2 mg and 4 mg of atropine sulfate on 12 volunteer helicopter pilots suggest atropine, particularly the 4-mg dose, causes a variety of decrements.

Flight performance assessments made by computer and a safety pilot showed most of the maneuvers were degraded on at least one parameter as a function of atropine. Control accuracy of altitude, airspeed, and roll-out heading were reduced by atropine across both left and right standard-rate level turns; and turn rate and vertical speed were influenced by atropine in the left turn. Altitude and heading control were reduced by 4 mg of atropine in the straight-and-level maneuvers. Control of slip was reduced by the administration of 4 mg atropine during the straight climb only in the afternoon, while heading and level-off altitude in this maneuver suffered during both morning and afternoon flights. Heading control also was degraded by atropine in the straight descent across both morning and afternoon flights. Accurate control of the roll parameter was compromised after administration of 4 mg of atropine during flight performance of steep turns in the afternoon.

Measures of airspeed and vertical speed evidenced atropine-related reductions during performance of the standard-rate climbing turn (under 4 mg), and there was a tendency for control of pitch to have been compromised by atropine as well. Control over airspeed, approach angle, and rate of closure while descending into the confined area was degraded by the presence of atropine, with the last two measures revealing decrements under both 2 mg and 4 mg. Also, there were reductions in the ability to accurately maintain precise vertical-ascent heading, hover altitude, and drift control during the out-of-ground-effect hover maneuver while under the influence of 2 mg and 4 mg of atropine. Finally, airspeed control suffered significantly as a function of 4 mg of atropine while subjects were performing an instrument landing system approach at the conclusion of each flight.

The computerized scoring system revealed most of these dose-related effects were attributable to the larger dose (4 mg) of atropine, whereas the smaller dose (2 mg) generally did not differ significantly from placebo. However, the safety pilot assessments of pilot performance often indicated both the 2-mg and the 4-mg doses of atropine were associated with lower performance than was observed under placebo. Drug-related performance degradations tended to occur rather quickly (within 30 minutes), and some lasted a long time (more than 7 hours). The decrements that occurred in the higher altitude maneuvers

suggested flight performance would suffer largely from unstable control of heading and airspeed in addition to a variety of other accuracy reductions. None of these maneuvers at higher altitudes appeared to present severe hazards to safe flight under relatively low stress conditions (good weather, no emergencies, etc). However, the data suggested flight operations conducted close to the ground which required very precise control over the aircraft were compromised significantly by atropine (mostly under the 4-mg dose). One subject would have crashed in the confined area on the 4-mg day if not for safety pilot intervention. Another couldn't hover under the influence of the 4-mg dose.

Vision testing revealed increases in pupil diameter and the likelihood of phorias after atropine administration. Also, there were decreases in accommodative power and both near and distant contrast sensitivity. Four of the 12 subjects broke visual fusion which indicates they were experiencing problems with double vision. Three subjects complained verbally of this problem, and one of these said he kept one eye closed during the afternoon of the 4-mg dose-administration day so he could fly the helicopter. The increases in pupil diameter cause increased problems with visual sensitivity to sunlight. The changes in accommodation after the 4-mg dose suggested subjects would probably experience problems reading standard tactical maps, and the reductions in contrast sensitivity raise the possibility some pilots may have difficulties recognizing targets, landmarks, and/or hazards to safe flight.

Evaluations of resting electroencephalographic (EEG) activity revealed atropine-induced central nervous system sedation, particularly under the 4-mg dose. It is noteworthy that most of these effects persisted 8 hours or more postdose. Such EEG changes help to explain many of the performance effects found under 4 mg atropine in terms of increased drowsiness and slower reactions.

Event related potential testing showed atropine generally reduced the amplitude of the N75 component, while the P100 component was affected only in the evening. These results suggest atropine initially (at peak levels) was interfering with visual acuity and was producing some general sedation, while also increasing the response to incoming light because of pupil dilation. In addition, there may have been some shifts of attention. Taken together, these effects generally suggest atropine produces decrements in visual stimulus registration, but the operational impact of these findings has yet to be established. The single cognitive ERP task (P300) revealed a latency shift and an amplitude reduction which suggested the subjects' ability to quickly and attentively process information was degraded, especially by the 4-mg dose. These data support what was observed with the performance evaluations.

Performance assessment battery testing indicated that atropine will affect visual search, logical reasoning, quantitative ability, short-term memory, and psychomotor response time. Both reaction time and accuracy were affected on three of the five tasks (logical reasoning, digit recall, and four-choice serial RT), whereas only the speed of responding was affected on the other two (six-letter search and serial math). Apparently subjects were attempting to preserve the accuracy of performance by slowing the rate of performance, but this strategy was often not completely effective. Although overall performance improved with increasing time from dose, response speed typically was degraded at both 3.5 hours and 9 hours postdose. Where response accuracy was concerned, there were typically improvements by the time of the later test session (9 hours). These results suggest some individuals may be able to avoid certain types of atropine-related performance problems in self-paced tasks if speed is traded for accuracy. However, this strategy will not be feasible for machine- or environmentally-paced tasks (e.g., responding to emergency situations).

Psychomotor tracking assessments revealed a number of general disturbances in tracking accuracy as a function of atropine. On the easiest test, there were general degradations in tracking performance as a function of the larger dose of atropine regardless of the intensity of a secondary distraction task. Also, the 4-mg dose was associated with reductions in responses to the secondary task. On the intermediate test, there were reductions in tracking performance under the larger dose only during the session at which atropine levels were greatest. Also, there were decrements in responses to the most demanding form of the secondary task during the noon session under the influence of both the 2-mg (marginally) and the 4-mg dose of atropine. On the most difficult test, there was reduced tracking accuracy as a function of the larger dose of atropine, again, during the noon session only (when atropine levels were highest). However, there were no atropine-related effects on responses to the secondary distraction task. It is worth noting that atropine did not appear to impact the accuracy of responses to the secondary distraction tasks associated with any of these three tracking tests. Apparently, subjects often just didn't make any response at all to the tones rather than making an incorrect response on this part of the test. These results support a suggestion made earlier after reviewing the cognitive data. When subjects were not permitted to pace the task themselves, the 4-mg dose of atropine often impacted the accuracy of performance. Subjects may not be able to accurately track a target or perform other machine- or event-paced tasks well after the 4-mg dose of atropine, especially when precise performance is required soon after the administration of the dose.

Subjective observations often revealed transient personality changes, particularly under the influence of 4 mg. Some subjects became irritable and impatient, others became quiet and withdrawn. Often there was a variety of other complaints about the effects of the 4-mg dose, whereas the 2-mg dose seemed to have much less of an impact.

Atropine sulfate, administered in any doctrinal amount, can be expected to affect tasks requiring visual acuity and precise flight control. Also, there will be transient personality changes in some individuals. When doses larger than 2 mg are administered, effects will be especially noticeable, and the scope could expand to include all tasks involving elements of rapid mental processing, especially where complex combinations of judgment and time-sharing are involved. Some of the vision data suggest pilots may have problems with map and instrument reading, whereas the tracking data implies less responsiveness to task demands under 4 mg atropine. The EEG data shows that atropine exerts sedative effects which may lead to reduced alertness and vigilance, particularly under the larger dose. Helicopter aviators are at greatest risk in complex operations close to the ground from within 30 minutes to several hours (probably not more than 9 hours) following a 4-mg dose. Progressive feelings of tiredness and ill-temper or apathy related to atropine may exacerbate these performance decrements in a more demanding operational environment. All of this information combined with the analysis of flight performance suggests a helicopter pilot could mistakenly inject up to 4 mg atropine and still safely return to base if he is not required to handle serious in-flight emergencies, perform overly-taxing secondary tasks, or execute maneuvers which require very precise aircraft control (i.e., formation flight or confined-area operations). However, his performance should be considered seriously impaired. Also, while the data collected under the smaller dose presents only limited cause for concern, even 2 mg of atropine likely will contribute to the sorts of alcohol-induced decrements for which "12-hours-from-bottle-to-throttle" is required even after consumption of a single alcoholic beverage (Department of the Army, 1986).

Based upon these results with up to 4 mg, it can be expected that 6 mg of atropine, while not life-threatening in and of itself, will lead to a variety of performance problems which will jeopardize the safety of aircraft and crews. The most prudent course of action after exposure to 6 mg of atropine sulfate would be to land as quickly as possible, preferably at base, and wait for most of the drug's effects to subside (at least 12 hours).

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Note

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Acknowledgments

The authors wish to express special appreciation to the helicopter pilots who participated in this investigation. Without their time, effort, and dedication, the data reported here could not have been collected.

Additionally, this study would not have been possible without extensive technical and professional support from a variety of personnel. Ms. Gloria Kennedy performed most of the subject recruitment and processed a large amount of the routine paperwork to keep things running smoothly. SGT Norman Pearson provided supervision for the technical staff, preparation and maintenance of laboratory equipment, and helped to ensure accurate test scheduling. SPC Jim Chiaramonte and SPC Doug Baer assisted with all aspects of experimental support, and both served as operators for the Aircraft In-flight Monitoring System in the UH-1 during test flights. SPC Vadankumar Patel provided general technical support and helped to monitor data which was telemetered from the UH-1 to the Laboratory. SPC Marvaley DeCambre monitored all radio transmissions from the UH-1 and OH-58 in order to contribute to the safe execution of the investigation.

CPT William Burgin flew the OH-58 helicopter which was used for data retransmission and as a safety "cover ship" during every flight during the investigation. Concurrently with his responsibilities as an aviator, he also handled a vast array of administrative and logistical support for the research team. West Point Cadet Antoine Freche spent most of his time with the Laboratory serving as a safety observer from the OH-58, and he assisted with portions of the data collection effort as well.

LTC Philip Taylor prepared the atropine sulfate injections and labelled each one in order to maintain the "blinded" experimental procedure. MAJ Glenn Mitchell, Chief of the Crew Life Support Branch, ensured the presence of flight medics, cardiopulmonary technicians, laboratory technicians, and other personnel responsible for physiological prescreening and monitoring. SSG Jose Rosario, SGT Frank Guardiani, SSG Lonnie Mills, SGT Joe Burke, SPC Rod Scott, SPC Frank Santulli, and SPC Suzanne Barnes all contributed significantly to the safety of our research participants.

Vision testing was accomplished with the assistance of Dr. Roger Wiley, Sensory Research Division, who provided support in terms of advise, instrumentation, and personnel. Mr. Simon Grace and SSG Nonilon A. Fallaria routinely assisted with the administration of numerous vision tests.

Personnel in Research Systems Division provided extensive technical support with instrumentation, calibration, data collection, and computer analysis. Mr. Howard Beasley, Mr. Allan Lewis, CPT Anthony Mitchell, Mr. Bob Dillard, Mr. John Hapgood, Mr. John Jenkins, and Mr. Phillip Johnson all contributed significantly to the research effort by installing and maintaining video and physiological telemetry systems, aircraft-mounted cameras, a modified aircraft intercom system, a variety of physiological monitoring instrumentation, and the computerized in-flight monitoring system. Dr. Heber Jones and Mr. Alford Higdon developed, implemented, and maintained the computer software used to download, store, and analyze objective flight performance data. Both of these individuals also provided immeasurable assistance in data analysis and interpretation.

Several Universal Energy Systems personnel, most notably Mr. Roger Christiansen, provided support in data collection on the computerized cognitive performance assessment battery, as well as some of the data analyses.

The significant fact that not a single flight was cancelled due to aircraft maintenance problems can be credited to the dedicated personnel of Sikorsky Support Services, Inc., at Cairns Army Airfield. These individuals responded rapidly and skillfully to potential problems. Their professionalism contributed substantially to the conduct of this investigation. Additionally, the air traffic controllers at Cairns AAF afforded our research aircraft priority handling which permitted strict adherence to the published testing schedule.

Finally, it should be recognized that research of this scale and importance would not have been possible without the support of the following command personnel: COL Michael Reardon, Research Area Director V, who authorized and maintained the fiscal support for this work; COL Dudley Price, USAARL Commander, and LTC Edmond Enloe, Deputy Commander for Administration, who ensured Laboratory-wide support for such a large scale investigation; COL J. D. LaMothe, Deputy Commander for Science, who ushered the protocol through the review, approval, and execution processes; Dr. Kent Kimball, Director of Programs and Plans, who initiated and fostered support for research of this type; and COL Gerald Krueger who was Division Director during the preparation of the final report.

Introduction

Statement of the problem

Aviators, like all soldiers, must maintain high levels of vigilance and skill to safely and effectively accomplish their missions; however, performance requirements of air-based operations differ markedly from ground-based operations. Clearly, the possible deleterious effects of any substance pilots encounter in flight are of great concern because of the potential safety hazards they create. Since the effects of atropine sulfate given in the doses prescribed by U.S. Army training doctrine as a chemical warfare antidote have not been documented in flight, it is essential to thoroughly examine safety concerns over such use, particularly as they relate to the effects of unchallenged atropine which may be administered after a perceived exposure to nerve agent (which, in fact, did not occur).

Background¹

Interest in research on the effects of atropine sulfate and other substances which fall into either the antidote category (as does atropine) or the pretreatment category (pyridostigmine bromide, for example) stems from the increasing likelihood the United States military must be prepared to counteract the potentially lethal effects of chemical agents. Because most "nerve agents" are primarily acetylcholinesterase inhibitors, the acetylcholine blockers like atropine are logical choices for counteracting the debilitating effects of exposure (Lobb, Phillips, and Winter, 1985). Atropine autoinjector kits have been procured for use in the field, and current U.S. Army training doctrine advises the self-administered use of up to 6 mg atropine (three 2 mg autoinjectors) in the event of organophosphate exposure.

Unfortunately, the use of atropine is not totally without problems; and, while the drug is the treatment of choice for the anticholinesterase effects of organophosphate poisoning, its effects on flight performance have not been thoroughly documented. Specifically, there is the potential that a soldier on the battlefield could fly into a cloud, mistakenly perceive he/she had been exposed to nerve agent, and subsequently inject

¹A more extensive background is available in Simmons et al. (1989).

atropine. The operational impact of such a misjudgment requires assessment.

Time course of atropine

Kalser and McLain (1970) examined the time course of atropine (N-methyl atropine and 2,4-¹⁴C-labeled atropine) in the blood, urine, and expired air of four subjects who had received 2 mg via intramuscular (i.m.) injection. Blood samples were collected every 5 minutes for the first hour; electrocardiograms were sampled at the same interval. Following the first hour, blood sampling was discontinued and heart rate was determined using pulse counts. Samples of expired air were collected at 15-minute intervals during the first 2 hours and at 30-minute intervals during the third hour. Urine samples were collected on an hourly basis during the first 8 hours and pooled samples were taken at 12, 24, 36, and 48 hours.

Transient bradycardia was seen in three subjects. Heart rate was maximal at 15 to 50 minutes; peak blood levels (of atropine) occurred during the same period. Overall, the temporal patterns of heart rate and blood levels were similar, rising within 5 to 15 minutes, peaking between 15 and 50 minutes, and decreasing slightly by 1 hour. Maximal concentration in expired air occurred at 75 minutes, and maximum concentration in urine occurred at 120 minutes. After 4 hours, when 1 subject had reported a return of adequate saliva flow and pulse counts indicated the tachycardia had subsided, 50 percent of the atropine had already been excreted. After 24 hours, between 87 and 93 percent of the initial dose had been excreted into the urine; and, after another 24 hours, only an additional 1.5 percent was excreted. Thus, it may be concluded, atropine effects occur rather quickly (as early as 15 minutes) and are of relatively short duration (subsiding substantially within 4 to 24 hours).

Effects of atropine on general physiological and psychological functioning

A summary of the effects of unchallenged atropine administration (i.e., atropine in the absence of organophosphate agents) indicates a number of potential physiological and psychological decrements (Lobb, Phillips, and Winter, 1985). Subjects may suffer from reduced alertness and increased anxiety due to the respective hypotensive effects and visceral symptoms of atropine administration. Atropine inhibition of sweat secretion increases the probability of reduced heat tolerance and impaired ability to eliminate toxic substances. Reduction in visual acuity may produce problems in the performance of visual

tasks such as map reading or instrument monitoring. Atropine-induced pupil dilation may result in photophobia. Vision may be blurred to the extent writing is hampered. Central nervous system (CNS) effects of atropine may cause dizziness and loss of equilibrium that could, in turn, impair ability to maintain psychomotor control (e.g., three-axis control while flying a helicopter). Furthermore, unchallenged atropine in high doses could lead to memory and information-processing impairments ultimately resulting in loss of attentiveness, impaired judgment, and poor decision-making. The reduction in salivation could lead to impaired speech and communication.

Miles (1955) conducted studies on the effects of 2 mg of atropine i.m., and found there was commonly reduced sweating and increased dryness of mouth, losses in visual acuity at short ranges, impaired physical efficiency during intense effort, increased pulse rate, and depressed CNS functioning; although, there was wide variation among individuals. However, subjects were not affected to the extent performance on normal visual, mental, or physical tasks, performed in a temperate environment, was seriously impaired.

Cullumbine, McKee, and Creasey (1955) arrived at similar conclusions after conducting an investigation in which subjects were administered intramuscular injections of 2 mg, 3 mg, and 5 mg atropine. Dryness of the mouth and throat with difficulty in swallowing were the primary complaints associated with the 2 and 3 mg doses, whereas the 5 mg dose produced additional complaints of dizziness, tiredness, reading difficulty, and problems with urination. Objectively, pulse rate was accelerated in a dose-dependent fashion, reaching peak rate at about 30 minutes. Systolic blood pressure was significantly reduced in response to the 3 mg and 5 mg doses, whereas diastolic pressure was increased in response to only the 2-mg dose. The Fitness Index Pulse, a measure of cardiovascular response to exercise, was reduced after the 2-mg or 5-mg dose of atropine, indicating atropine administration prior to exercise places a greater than usual strain on the cardiovascular system. Finally, the administration of 5 mg atropine significantly increased the length of time it took to run 100 yards. On the basis of these results, the authors concluded 2 mg of atropine could be administered without hesitation in cases where organophosphate poisoning was suspected, but 5 mg could produce "embarrassing effects" in the absence of such poisoning.

A study conducted by Vojvodic, Rosic, and Vojvodic (1967) further supported the earlier findings of other investigators with regard to dryness of the mouth and throat; drowsiness; and, for some subjects, the vertigo and numbness produced by 2 mg of atropine. Furthermore, these authors noted the tachycardia which typically follows atropine injection. Seppala and Visakorpi

(1983) reported many of the other typical antimuscarinic effects of atropine using oral doses of 0.85 and 1.70 mg. The occurrence of pupil dilation was evident as early as 1 hour postdose, and this effect lasted for up to 4 hours. The 0.85-mg dose caused slight initial bradycardia at 1 hour followed by insignificant tachycardia at 2 hours. The 1.70-mg dose produced initial effects no different from the smaller dose; however, the tachycardia which occurred beyond 1 hour postdose was significantly greater than either the tachycardia produced by the smaller dose or that produced by the placebo. Near point of vision was changed in a dose-related fashion and was significantly different from placebo at 2 hours postdose for the 0.85-mg dose and at 1, 2, and 4 hours postdose for the 1.70 mg. Furthermore, the authors found atropine affected coordination and equilibrium. The lower dose exerted the greatest effect on equilibrium in the eyes-open condition, and the higher dose had the greatest effect in the eyes-closed condition.

Effects of atropine on work performance and thermoregulation

A potentially significant problem with the use of atropine centers around the reduction in sweat secretion commonly seen with the drug. This effect is serious under some circumstances because body heat is only dissipated through the processes of radiation, convection, and/or evaporation, and atropine reduces the rate of evaporative heat loss (Sawka et al., 1984). Of course, the relative importance of each mechanism in proper thermoregulation depends upon the environmental factors of temperature, wind, and humidity, so the greatest level of atropine-induced, heat-related impairment would be observed under hot, dry conditions in which evaporation would ordinarily be the primary cooling mechanism.

Cadarette et al. (1986) clearly illustrated the importance of environmental considerations in examining the effects of atropine. The authors studied the effects of 2 mg atropine and placebo upon the ability of 6 subjects to walk on a treadmill for 100 minutes under 3 different environmental conditions (hot-dry, warm-moderate, and warm-wet). Each environment created roughly equivalent levels of thermal stress as indicated by similar wet bulb globe temperature (WBGT) indexes. The subjects were all heat acclimated prior to testing. Atropine reduced sweating and increased both heart rate and skin temperature in all three environments. Overall, the most problematic atropine effects were seen under the environmental condition which relied most heavily on evaporative cooling. After atropine, the time spent on the treadmill was reduced by 26.5 minutes in the hot-dry environment. Mean exposure times were 73.5 minutes in hot-dry, 90.2 minutes in warm-moderate, and 100 minutes in warm-wet. Only one subject completed the exercise under hot-dry conditions,

while two were removed because of elevated rectal temperature, and the other three suffered syncope.

An earlier investigation, designed to study both the effects of environment as well as the impact of acclimatization, provided support for the Cadarette et al. findings. Cullumbine and Miles (1953) exposed subjects to two different environments and reported performance under atropine in a hot-dry environment was worse than in a warm-moist environment; however, performance could be substantially improved in the hot-dry environment if an acclimatization period was permitted. These results combined with those of Cadarette et al. (1986) clearly indicate the necessity of considering the interactions between environment and drug administration when contemplating the effects of atropine. Also the importance of permitting subjects to acclimatize to higher thermal stress should not be overlooked.

Effects of atropine on vision and performance

Numerous studies have determined the effects of a variety of doses of atropine upon both vision and performance. Moylan-Jones (1969) investigated the effects of 6 mg atropine i.m. on 23 subjects and documented the occurrence of drowsiness, mild perceptual disturbances, and some performance impairment. Three separate placebo injections were administered 20 minutes apart on the first day. Three injections of 2 mg atropine each were given on the second day. No injections were given on the third day. Subjects were administered tests on number facility, fox-hole digging, field medicine, map reading, compass use, marksmanship, and tire-changing speed during two sessions immediately following the second injection and 2 hours 25 minutes after the third injection. Results indicated a general reduction in levels of alertness and a high incidence of mydriasis on the atropine day. Several subjects also reported minor hallucinations. Digging performance was degraded overall and number facility was impaired on the afternoon of the atropine day. Furthermore, the field medical team was less efficient after atropine administration; and, map and compass reading were degraded on the morning of the atropine day. The drug did not significantly affect shooting accuracy or the speed with which tires were changed. Overall, the author concluded physical tasks would either be abandoned completely or delayed, whereas tasks involving skill would be performed less efficiently under atropine than under normal circumstances.

The performance-impairing effects of atropine were corroborated in an investigation using placebo, 2, and 4 mg of atropine per 70 kg body weight in 10 male subjects (Jampolsky et al., 1984). The large dose of atropine significantly impaired tracking ability when subjects were tested 2.5 to 3.0 hours

postdose, but not 0.5 to 1 hour postdose. This finding lends support to the earlier finding that number facility was not degraded immediately after atropine dosage, but was degraded 3.25 hours later (Moylan-Jones, 1969). Additionally, Jampolsky et al. (1984) found the 4-mg dose produced a great deal of fatigue. Most of their subjects went to sleep on the afternoon of the 4-mg day and had to be awakened to perform the final tracking task. Thus, it was no surprise to find impairments in performance requiring physical effort.

Effects of atropine on the performance of tracking tasks have been documented further in other studies. Holland, Kemp, and Wetherell (1978) used a pursuit rotor task as one of the dependent measures in a study designed to assess both the separate and combined effects of 2 mg atropine and 5 mg diazepam. The atropine injection caused poorer performance than either placebo or diazepam when subjects were tested 90 minutes after dose administration. Partial support for these findings resulted from a Baker et al. (1983) study in which 2 mg atropine per 70 kg body weight significantly degraded pursuit tracking performance on a complex tracking task, but not on easier tasks, at 30 and 240 minutes postdose. Subjects appeared to be affected only when under the higher levels of stress incurred as a result of increased difficulty. Here again, it seemed the fatigue-inducing effects of atropine were interacting with any other debilitating effects the drug may have had. Another study, by Penetar and Beatrice (1986), failed to replicate the above findings with only 2 mg atropine per 70 kg body weight, but indicated 4 mg/70 kg body weight caused a significant reduction in tracking ability both at 30 and 150 minutes postdose under dim illumination. Also, a significant reduction was seen at 150 minutes postdose under bright illumination.

A task which has some similarity to tracking tasks and which certainly has relevance in a military context is shooting a rifle. The effects of a 2 mg oral dose of atropine upon the shooting performance of 12 military cadets were evaluated in double blind fashion by Seppala and Visakorpi (1983). Subjects fired 10 rounds at a target during each of 2 sessions, the first of which was subject-paced and the second of which was timed (5 seconds were allowed per shot). Atropine had no significant effect upon accuracy during the self-paced session, but caused a significant decrement during the timed session. These findings are consistent with those of Vojvodic, Rosic, and Vojvodic (1967) who reported firing at bust silhouette targets at 30 meters 1 hour to 1.5 hours postdose was significantly impaired by a 2-mg dose of atropine. However, they are at odds with the earlier findings of Moylan-Jones (1969), who did not detect differences in shot groupings after 6 mg atropine; and those of Robinson (1953) who found 2 mg atropine did not affect marksmanship in firing 30 rounds at 200 yards. It should be noted, though, these

differences could have resulted from the use of different types of targets, variations in distance, task timing (relative to dose), inconsistencies in the actual tasks themselves, or inconsistencies in scoring procedures rather than absolute differences in the effects of atropine.

Performance on tasks having strong visual components may be affected by either the sensory-level degradations caused by atropine or the CNS effects of the drug. Numerous studies have been conducted on the effects of atropine upon the visual system. A very short review of relevant material is cited here. Headley (1982) surveyed the literature concerning the effects of atropine and pralidoxime chloride upon visual functioning and other variables in man. His review of the effects of atropine on vision revealed 2 mg of injected atropine produced increases in pupil size which ranged from 0.85 mm to 2.0 mm at 6 hours postdose, whereas 4 mg of atropine produced a 50 percent increase in pupil size after only 2 hours. Further, 2 mg atropine increased the distance at which finely-printed material was legible to 100.1 mm from 73.8 mm 3 hours postdose. Visual near-point dropped to 5.75 diopters from approximately 8.5 diopters over 6 hours with 2 mg atropine, and injections of up to 3 mg altered accommodation amplitudes. Visual fatigue lasted up to 6 hours after the administration of a 4-mg dose. Subjective reports of problems with near vision indicate atropine-induced difficulties are dose-related. One hundred percent of subjects reported problems after 4 or 5 mg, whereas only about 40 percent of subjects reported problems after 2 or 3 mg.

Rubin (1956) found 2 mg of atropine did not significantly affect either the absolute threshold or the time course of dark adaptation. An investigation by Kay and Morrison (1987) confirmed the effects of atropine on pupil diameter and accommodative range. Additionally, while contrast sensitivity to stationary patterns was unaffected by 2 mg atropine, contrast sensitivity to moving patterns of low spatial frequencies was impaired for up to 6 hours. Such effects on movement sensitivity could explain some of the earlier degradations discovered with regard to tracking performance.

Because of the confusion over whether atropine-related performance degradations are produced by the effect of atropine on vision or the central effects of the drug, Baker et al. (1983) conducted a set of investigations in which both vision and tracking performance were examined. In the first study, 10 subjects were injected with 2 mg atropine per 70 kg body weight and subsequently administered a battery of vision tests. In the second study, 6 subjects were injected with 2 mg atropine per 70 kg body weight and then tested on 2 tasks which required rapid accommodation changes, visual search, motor responses, and some short-term memory. Overall, while contrast sensitivity, pupil

size, and accommodation were affected, performance on the accommodative change task and the visual search task did not reveal atropine-induced impairments. These findings could be interpreted to suggest the effects of atropine on vision and tracking are separate. Many of the same authors who conducted the preceding investigation later found tracking errors on a different type of task were increased by 4 mg atropine per 70 kg body weight. These decrements followed a similar time course to observed changes in pupil size, accommodation, and near visual acuity (Haegerstrom-Portnoy et al., 1987). These results led the authors to postulate the existence of spherical aberrations associated with increased pupil diameter which could have made the target difficult to see and, subsequently, affected tracking performance on a test performed at optical infinity.

Effects of atropine on cognitive performance

Other studies of the effects of atropine upon performance focused primarily on cognitive aspects since many operational tasks possess a strong mental component. However, as can be seen in the following summary of these studies, the findings are often inconsistent from one investigation to the next. Grammatical reasoning was found to be significantly affected (reduced number of problems attempted) after the second exposure to 2 mg atropine in one study (Banderet and Jobe, 1984), marginally impaired ($p < 0.10$) by 2 mg of atropine in another study (Banderet et al., 1986), and completely unaffected by 2 mg of atropine in a third study (Holland, Kemp, and Wetherell, 1978). Pattern comparison was unaffected by the same 2-mg dose, whereas coding performance was impaired under the second atropine exposure in one study and under the single atropine exposure in another (Banderet and Jobe, 1984; Banderet et al., 1986). Arithmetic ability was affected by a 2-mg dose in one study (Holland, Kemp, and Wetherell, 1978), but reportedly unaffected by a 3-mg dose in another (Marzulli and Cope, 1950).

The effects of atropine on reaction time were inconclusive in one investigation (Marzulli and Cope, 1950), not significantly different (choice reaction time) from hyoscine or placebo in another (Anderson, McGuire, and McKeown, 1985), significantly degraded in comparison to placebo or diazepam in a third (Holland, Kemp, and Wetherell, 1978) and significantly improved by 0.85 mg oral atropine in comparison to either a placebo or a 1.70-mg dose in yet another (Seppala and Visakorpi, 1983). Backward digit span (as in the Wechsler Adult Intelligence Scale) was significantly degraded by administration of 0.6 mg atropine in a study by (Anderson, McGuire, and McKeown, 1985). Forward digit span was degraded by 0.85 and 1.70 mg oral atropine in still another investigation (Seppala and Visakorpi, 1983). However, 3 mg atropine i.m. had no effect on digit recall

(presumably forward digit span) in an investigation by Marzulli and Cope (1950). Two experiments reported by Wetherell (1980) were somewhat contradictory. In one, forward digit span was significantly degraded by 2 mg atropine administered i.m. In the other study, 2 mg atropine when administered orally did not affect either type of digit span. Tests of vocabulary, self-reported mood, orientation, automated series, rhyming, word memory, letter cancellation, and maze tracing were all resistant to any deleterious effects of 0.6 mg atropine i.m. (Anderson, McGuire, and McKeown, 1985). Finally, Marzulli and Cope (1950) detected no atropine-induced reductions in speed of reading aloud.

Effects of atropine on the electroencephalogram

In attempts to determine the effects of atropine on the central nervous system, as opposed to the peripheral nervous system, some investigators have collected electroencephalographic (EEG) data on subjects receiving various dosages. These data are of interest here because they offer insight into the effects of atropine on subjects' general level of arousal or activation (which would exert some impact on performance). A review of many of these studies by Longo (1966) reported the usual therapeutic doses of atropine ranging from 0.5 mg to 2 mg generally do not produce noticeable effects, with the exception of some modest respiratory stimulation. However, when the amount of atropine exceeds 10 mg, the central effects of the drug become manifest, even though the peripheral effects do not appear to intensify.

Among the central effects and cognitive effects reported over the range of doses reviewed were: 1) a reduction in concentration and memory with between 0.4 mg and 10 mg of the drug which was sometimes characterized as a "broadening of attention" (p. 996); 2) an increase in drowsiness and sleepiness with doses as low as 2 mg; 3) a peculiar excitatory effect which could be characterized as apprehension with doses at or below 10 mg, and as confusion combined with excitation at higher doses; 4) loss of coordination with doses higher than 10 mg; and 5) hallucinations with very large doses of atropine.

Longo's (1966) review of electroencephalographic effects revealed reasonable consistency among the findings from various studies. Specifically, the author reported atropine in doses of 1 mg to 5 mg caused an increase in slow-wave activity which concurrently caused reductions in faster alpha (8-12 Hz) activity. Also, some patients evidenced a reduction in the degree of alpha blockade during eyes-open under the influence of 1 mg and 9 mg atropine. Furthermore, Ostfeld, Machne, and Unna (1960) reported 10 mg of atropine was associated with a decrease in EEG arousal following both single and repetitive photic

stimulation, as well as a reduction in the percentage of alpha activity (because of frequency slowing) after 2 hours postdose. Finally, a preliminary study conducted by Himwich (1954) produced results partially consistent with those reported above. The author concluded atropine (3-8 mg) increased the amplitude of alpha waves, reduced eyes-open alpha blockade, and enhanced the amount of slower EEG activity which is often associated with drowsiness.

Effects of atropine on flight performance

Since aviators are at particular risk in potentially performance-degrading environments, an examination of the effects of atropine upon flight performance was undertaken by the U. S. Army Medical Research and Development Command. The first two studies were done in flight simulators. The simulator permitted a detailed examination of a series of flight tasks, all of which were flown by reference to instruments only.

In the first one, Dellinger, Taylor, and Porges (1987) studied the effects of 0, 0.5, 1.0, 2.0, and 4.0 mg of atropine/75 kg body weight on 20 male general aviation instrument student pilots. The subjects flew a fixed-base, fixed-wing instrument simulator while periodically performing a secondary Sternberg memory search task. The primary flight task consisted of entry into a holding pattern, maintaining three separate holding patterns, and executing an instrument landing system (ILS) approach while measures of altitude, turn rate, localizer tracking, and glideslope tracking were sampled by computer. Following two training sessions, there were five experimental sessions (one per dose), each 1 week apart, consisting of one baseline and five postinjection simulator flights. The dependent measures consisted of six root mean square (RMS) deviations, based upon previously mentioned measures, computed from each flight.

There were no differences between placebo and 0.5 mg, only one difference after the 1.0 mg, some differences between placebo and 2 mg, and significant increases in all RMS errors by the time of the fifth postinjection flight with 4 mg. The increase in RMS errors produced by the 4-mg condition began within 1 hour and either continued to climb or leveled off for the remaining flights. Performance on the Sternberg task did not differ among the treatments. The authors concluded 2 mg of atropine could be expected to cause performance degradations within 100 minutes postinjection, but 4 mg atropine could be expected to produce substantial decrements within 60 minutes postinjection. The decrements produced by the larger dose would probably last for more than 3 hours. Performance effects lagged behind physiological effects by about 30 minutes; so, possibly, aviators

could use the experience of tachycardia and decreased salivation following atropine injection to warn themselves of oncoming performance degradations. In summarizing that research, Taylor et al. (1985) suggested further studies "using Army aviators flying Army tactical scenarios...at the higher doses of atropine sulfate (i.e., 2.0 and 4.0 mg)..." were needed.

Building upon that recommendation, the second aviation study conducted by researchers at the U. S. Army Aeromedical Research Laboratory (USAARL) (Simmons et al., 1989) examined the effects of atropine on the simulator flight performance of 12 Army helicopter pilots flying a 2-degree-of-motion (pivotal) instrument helicopter simulator twice per day under each of 3 experimental conditions (placebo, 2 mg atropine, and 4 mg atropine). Atropine dosage levels were not adjusted according to each subject's body weight since the standard atropine autoinjectors issued to soldiers are not individualized according to body weight. The simulator flights were interspersed with laboratory tests on vision, cognition, psychomotor tracking, and psychophysiological functioning. The flight tasks consisted of a series of "upper air work" maneuvers followed by an instrument takeoff, navigation to a designated airport, holding at an approach outer marker, and an ILS approach to landing. Subjects executed these maneuvers while measures of heading, altitude, airspeed, climb rate, turn rate, localizer, and glideslope were collected by computer.

There were atropine-induced degradations in subjects' abilities to maintain assigned heading, altitude, airspeed, and vertical speed during a straight-and-level segment; decrements in maintenance of vertical speed during a climbing turn; atropine-related decreases in precision control of aircraft heading during a set of maneuvers calling for specified headings, altitudes, and airspeeds for designated periods of time; and marginal ($p=0.0541$) atropine-related increases in ILS localizer tracking errors. Most frequently, significant differences were found between the placebo and the 4-mg dose. Cognitive and tracking effects indicated atropine caused a general slowing of performance which allowed subjects to maintain accuracy on the cognitive tests, but served to decrease performance on the tracking test. Findings regarding the electrophysiological measures revealed subjects were probably experiencing atropine-related problems in both stimulus identification and information processing. The statistically significant performance effects on flight, cognitive, tracking, and electrophysiological measures were not, however, of sufficient magnitude to preclude the safe conduct of an actual in-flight study to assess many of the operational effects of atropine use among helicopter pilots.

Military significance

Recent intelligence and published changes in Warsaw Pact military doctrine lead analysts to believe there is a high probability an enemy will use chemical and biological agents in future armed conflicts. In the past, public attention was focused on chemical deployment and its use by the Soviets and their counterparts in Southeast Asia and Afghanistan (Haig, 1982) as well as its use by Iran and Iraq in conflicts between those two countries (Newhouse, 1987). More recently, the American public and members of the U. S. Armed Forces have faced a stark reminder of the imminent threat of chemical conflict while attempting to curtail Iraqi aggression toward other Middle East countries. Iraq possesses several thousand tons of chemical agents, including mustard and nerve gas (Scicchitano, 1990), and there is considerable evidence that Iraqi forces would use these weapons without much hesitation.

GEN (Ret) Frederick J. Kroesen; Vice Chief of Staff, U. S. Army, 1978-1979; Commander-in-chief, U. S. Army, Europe, from 1979-1983, recently (1989) outlined the threat of chemical warfare to the Association of the United States Army Institute of Land Warfare:

...the threat has become increasingly serious and should be of great concern to all. A decision to employ American military forces almost anywhere in the world cannot be made today without cognizance of the fact that they could be subject to chemical attack. Our Army's capability to deter such an attack, or to survive and continue effective operations if deterrence fails, is the proposition that must be addressed fully by our government. (p. 12)

Thus, the threat of chemical weapons, as well as both conventional and nuclear weapons, is considered in U. S. military doctrine.

Army aviators are at serious risk in the chemically contaminated environment since even exposure to nonlethal riot control agents, such as tear gas, in the air can disrupt their ability to maintain aircraft control. Thus, in real terms, should aviators encounter a chemical agent, the potential outcome is failure of the mission and possible loss of aircrew and aircraft. While crews and passengers conceivably could don protective gear as needed, the inability of the pilot to turn from the flight task and the lack of sufficient room in helicopter cockpits to don a chemical defense (CD) protective clothing ensemble necessitate, in any chemical threat situation, the pilot must previously have donned the clothing. This is especially true for helicopter flight near the ground, as in terrain flight tactics conducted by

the U. S. Army. Thus, the ability of the pilot to effectively operate his helicopter while wearing a CD clothing ensemble is the first key to operational effectiveness on the chemically contaminated battlefield.

The second key to effective operation in a chemical environment is the timely use of antidote and pretreatment drugs (APD) which, at a minimum, can enhance the likelihood of the safe return of the crew and the aircraft. The Army has not settled on ideal compounds to permit efficient mission accomplishment even after exposure to chemical agents. Nor, for that matter, has the impact of antidotes on aviator safety been established.

Three compounds--atropine sulfate, pralidoxime chloride (2 PAM-CL), and pyridostigmine bromide--currently are under consideration by the military as APD; but, some of these have side effects which suggest a priori that effective mission accomplishment or safe flight may not be possible after receiving the normal doctrinal dose of these drugs. The research of Simmons et al. (1989) was the first phase (using a flight simulator) of a study to determine the effects of atropine in doctrinal doses on helicopter pilots in actual flight scenarios. This is a report of the second phase (using real aircraft). Such research is of critical importance to strategists, tacticians, and commanders who must plan for battles which may be fought under chemical warfare conditions. Specifically, these planners must consider that aviators could misperceive the presence of a chemical threat under battle conditions. They may then inject atropine and subsequently suffer from the effects of the antidote in and of itself. Thus, it is important to completely understand the effects of "unchallenged" atropine. If these drugs substantially degrade aviator and aircrew performance, significant changes to tactical plans may be required for both survival and mission success.

Objective

The purpose of this investigation was to assess in-flight performance of Army helicopter pilots who volunteered to have the chemical defense antidote atropine sulfate administered. The primary focus was to determine the effects of unchallenged doctrinal doses of atropine on the efficiency of pilots while accomplishing tasks required by operational flight scenarios. In addition, some of the psychomotor, cognitive, and psychological effects of atropine were examined.

Method

Subjects

Twelve male Army aviators in good health were used as subjects. Each subject had at least 20/20 uncorrected vision with less than 1.0 diopter of refractive error, possessed normal hearing, and was between the ages of 24 and 32 (mean=29.1). Each one received a complete physical examination to include a cardiopulmonary function test and a cardiac stress test. Furthermore, each was tested for atropine sensitivity prior to participation in the study. All participants were at least qualified in the UH-1 helicopter prior to selection for the study and were brought to currency during training flights. Additional demographic information is documented in Table 1.

Table 1.

Demographic information.

Subject number	Age	Height (in)	Weight (lbs)	Ethnic	Hand	Rank	Total flight hours	UH-1 flight hours
1	28	69	155	Cau	R	CW2	1700	80
2	31	70	168	Cau	R	CW3	2500	2500
3	24	64	141	Cau	R	CW2	677	55
4	31	70	160	Blk	R	WO1	505	485
5	30	65	135	Cau	R	CW2	2700	1000
6	30	68	145	Blk	R	WO1	420	420
7	32	74	230	Cau	R	CPT	365	320
9	29	72	192	Cau	L	2LT	325	280
10	30	66	150	Cau	R	WO1	660	60
11	31	72	198	Cau	R	CW2	914	876
12	24	74	180	Cau	R	2LT	175	60
13	29	74	210	Cau	R	1LT	295	295

Note: Subject no. 8 was disqualified for medical reasons prior to the first drug administration day.

Apparatus

Atropine sulfate

The 2-mg dose of atropine was prepared by dissolving 3.0 mg atropine sulfate (5 atropine sulfate hypodermic tablets, Lilly No. 17, 0.6 mg each) in sufficient sterile water for injection, U.S.P., to give a final volume of 1.50 mL. The resultant solution contained 2.0 mg atropine sulfate per 1.0 mL and the injection volume was 1.0 mL.

The 4-mg dose of atropine was prepared by dissolving 6.0 mg atropine sulfate (10 atropine sulfate hypodermic tablets, Lilly No. 17, 0.6 mg each) in sufficient sterile water for injection, U.S.P., to give a final volume of 1.50 mL. The resultant solution contained 4.0 mg atropine sulfate per 1.0 mL and the injection volume was 1.0 mL.

The placebo consisted simply of sterile water for injection, U.S.P. Once again, the injection volume was 1.0 mL.

Initial physical examination

The stress testing equipment consisted of a Marquette* computer-assisted system for exercise (CASE) interfaced with a Quinton* clinical research treadmill (model 18-60). Pulmonary testing was accomplished with a Gould* 5000 computerized pulmonary function laboratory.

Computerized in-flight performance evaluation

Two U. S. Army helicopters and a variety of integrated hardware and software were used to objectively evaluate pilot performance across a number of flight maneuvers. The primary aircraft, a U. S. Army JUH-1H utility helicopter (Figure 1), was modified to allow in-flight data recording of all flight instruments, warning systems, and control movements. An aircraft in-flight monitoring system (AIMS) (Mitchell et al., 1988) was mounted in the cargo compartment. Furthermore, the aircraft was equipped with three video cameras to permit behavioral monitoring of each subject, as well as the telemetry equipment described later, and three pieces of environmental or physiological monitoring equipment (two Wibget* model RSS-217 wet bulb globe temperature data loggers, and a Tektronix* model 414 portable patient monitor) which helped to ensure the safety of each participant. The secondary aircraft, an OH-58 (Figure 2), was

*See Appendix B.



Figure 1. U. S. Army JUH-1H helicopter.



Figure 2. U. S. Army OH-58 helicopter.

used as a safety cover aircraft and telemetry retransmission station. Both aircraft were manufactured by Bell Helicopter Textron.

The AIMS software consisted of an interactive data acquisition program in which operator requests and screen updates were handled on a time-available basis, whereas sampling occurred in real time. The analog-to-digital converter setup, the display routines, and the calibration software were customized for the flight profile used. The following parameters were monitored: 1) barometric altitude, 2) airspeed, 3) cyclic** fore-aft position, 4) cyclic left-right position, 5) collective** position, 6) antitorque pedal** position, 7) roll angle, 8) aircraft magnetic heading indicator, 9) pitch attitude, 10) X-axis (longitudinal movement) accelerometer, 11) Y-axis (lateral movement) accelerometer, 12) Z-axis (vertical movement) accelerometer, 13) vertical airspeed, 14) ILS localizer indicator (runway centerline), 15) ILS glideslope indicator (approach angle), 16) engine torque, and 17) maneuver start/stop point marker.

Specialized software was written for the Laboratory's DEC* VAX 11/780 computer system to read AIMS data tapes. The data were translated to interpretable units of measurement to facilitate subsequent data analyses. Additionally, the VAX software permitted calibration of flight parameters, storage of parameter samples from each maneuver, computation of RMS² error values, calculation of summary statistics, and production of finalized data files.

Safety pilot in-flight performance evaluations

In addition to the computerized scoring system, a safety pilot rated the performance of each subject on each maneuver using a specially constructed rating form. There was a separate

**Controls with which the helicopter pilot maneuvers the aircraft.

²The RMS error score was calculated in the typical fashion. The squared deviations of each sample from a predetermined standard were calculated, summed, and divided by the total number of samples. Then, the square root of this result was obtained so that deviations about the expected standard were expressed in units of the same magnitude as the units of measurement for the particular variable of interest. Thus, the procedure for calculating RMS errors is similar to the procedure for calculating standard deviations except that RMS error is calculated using differences from an ideal value rather than from a mean.

sheet for each maneuver on which the important flight parameters for the specific maneuver could be evaluated in terms of how well the subject remained within prescribed limits. The safety pilot simply circled the observed degree of deviation from the standard, and these were converted to a numerical scale for subsequent analysis. The same safety pilot was used for every flight.

Physiological monitoring

ECG data were collected with six Hewlett-Packard* disposable electrodes (14445A), three of which were connected to a Holter recorder (Hittman Medical Systems*, Compact IV-H) while the subject was in the Laboratory and to the patient monitor while the subject was on board the aircraft. The other three electrodes were used only for secondary monitoring while the subject was in the aircraft and were attached to the Telefactor* telemetry unit (described in detail later) so each subject's ECG data would be included with his EEG data. Additionally, throughout every testing flight, each subject's core body temperature was monitored continuously using a Yellow Springs Instrument Co.* rectal probe (model F-18480-701-120-A 12CM-BL15CM-PH, Series 700) connected to the patient monitor.

Vision testing

The visual battery for the study involved the administration of a series of standard diagnostic vision tests consisting of measures of refractive error, acuity, heterophoria, accommodation, near point of convergence, fusion, static contrast sensitivity, stereopsis, and pupil diameter. Refractive error was measured using both Humphrey* (model 520) and Topcon* (model RM-A6000) automatic refractometers. Distant visual acuity was measured with a Snellen eye chart displayed via a True* visual acuity (TVA) analyzer (model DM9012). Near visual acuity was measured with a miniature Snellen chart (Lebensohn, 1936) held 35 cm from the subject's eyes. Heterophoria (failure of the visual axes to remain parallel) was measured using the Armed Forces vision testing apparatus, near and distant (Cat. No. 71-21-40-64), for the determination of both vertical and lateral phorias at near and far positions. Accommodation and near point of convergence were measured using a Prince rule and an accommodation target. Fusion was determined using the Worth* four-dot test (Brightstar model 1619). The degree of static contrast sensitivity was measured with the Vistech* contrast test

system. Stereopsis was measured with the TNO³ test for stereoscopic vision (Lameris*), and pupil diameter was determined using a simple millimeter ruler. The light level, measured in footcandles, was determined at the outset of each session with a LiteMate* III photometer (model 504).

Electroencephalographic (EEG) testing

EEG data were collected from each participant using three separate systems depending on whether the specific test was 1) resting (eyes-open/eyes-closed) EEG followed by early component visual evoked response testing, 2) late component (P300) testing, or 3) in-flight monitoring of ongoing EEG activity. Both the resting EEG and the early component evoked response data were collected with a Cadwell Laboratories* Spectrum 32 brain mapping system interfaced to a 15-inch CRT for stimulus presentation. The P300 data were collected through a Cadwell Laboratories model 7400 evoked response system interfaced with the same CRT. For the sake of clarity, both the early and late component responses will be referred to as event related potentials (ERP).

The in-flight monitoring used a Telefactor* model TM100 encoder unit configured to address 8 of 16 channels. The TM100 encoder was configured either to transmit directly to a Telefactor model TM100-R receiver (if the subject was in the Laboratory) or to use an auxiliary transmission system located on board the helicopter (if the subject was in the aircraft). The auxiliary system consisted of an onboard Conic* model CTM-305K solid state transmitter with an output power of 13 watts. This transmitter sent data encoded by the TM100 from the testing aircraft to a receiver (DEI* model GPR-20) onboard the OH-58. The data then were retransmitted via another Conic transmitter (CTM-305K) and received in the Laboratory via a UHF/VHF antenna (Federal stock model AT-197A/GR) by a DEI model TR-711 receiver.

The encoded signals (received by either the TM100-R receiver or the TR-711 receiver) were decoded by a Telefactor model TM101-16D decoder, conditioned by a Telefactor model SC16-GO signal conditioner, and displayed using a Telefactor W/TV-16B reformatter connected to an Audiotronics* model 14VM939 monitor. The displayed signals (presented in strip chart fashion) were partially overlaid with a video record of the subject, and taped using a Panasonic* model PV-1730 VHS recorder. Additionally, a hard copy of the data was obtained by connecting the decoder

³TNO stands for "technisch natuurkundig onderzoek," and refers to the Netherlands Organization for Applied Natural Science Research in Soesterburg, The Netherlands.

output to the input panel of a Grass* model 78D polygraph. The system also accomplished hard-disk and tape storage of the data.

All EEG data were collected using Grass E5SH silver cup electrodes treated with chloride according to accepted procedures. All the Laboratory testing was conducted inside a dimly illuminated (25-watt incandescent bulb) sound-attenuated chamber. A standard interface plug was locally designed and built to minimize problems connecting the wiring from 25 separate electrodes to a variety of equipment.

Performance assessment battery

Selected subtests from the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR PAB) described in Thorne et al. (1985) were administered via microcomputer-based automated routines (Apple* II+ with a hard disk). Stimuli were presented on a remote color monitor as white letters on a black background. Responses were entered from a modified QWERTY keyboard for four of the five tests. The exception was the Wilkinson four-choice reaction time test administered via an additional (locally manufactured) stimulus/response apparatus upon which were located four LEDs forming a square and four corresponding pushbuttons. The data obtained from each subtest were recorded automatically during each test session in a format which was later used to create the finalized data file for analysis on a DEC VAX 11/780 computer. All testing sessions were conducted in a dimly illuminated, sound attenuated chamber.

Zero input tracking analyzer (ZITA)

The ZITA* (model Mk Xc), a programmable, dual-task compensatory tracking device, presented a fixed target and a laterally moving cursor on a self-contained 17- x 192-dot matrix display. The direction and duration of cursor movement were controlled with a joy stick located on the ZITA console. The console was additionally equipped with two pushbuttons used as response keys for a secondary auditory distraction task. For ease of test administration and scoring, the ZITA unit was interfaced with an Apple II+ microcomputer equipped with a hard disk. To minimize extraneous distractions, subjects were tested in a dimly illuminated, sound attenuated chamber identical to the ones in which the preceding tests were conducted.

Procedure

Overview

Each subject was brought into the Laboratory on a Monday morning and remained there until the completion of all testing. Participants were required to live in the Laboratory to provide appropriate medical monitoring and to preclude introduction of other drugs (such as alcoholic beverages or cold remedies, for example) during the study period. Subjects were free to smoke cigarettes and drink coffee, soft drinks, or water ad libitum when not testing.

Once a subject arrived at the Laboratory, informed consent (Appendix A) was obtained, relevant questions were addressed, and a complete physical examination was conducted to include a cardiac stress test, a pulmonary function test, and an atropine sensitivity test. After the physical examination, each subject completed initial training on the PAB and ZITA. After lunch, he was briefed on the in-flight evaluation and completed the first training flight. Following the flight, he was given another training session on PAB and ZITA, followed by EEG electrode attachment (Table 2). Electrodes were worn throughout the rest of the study.

Table 2.

Activity schedule for atropine study, phase II. Reception day.

0700	Introduction, project overview, volunteer agreement form signed
0730	Medical exam, pulmonary function, stress test, and atropine sensitivity test
1030	PAB training
1115	ZITA training
1230	Lunch
1325	Flight profile briefing
1355	Helicopter systems check
1405	Helicopter in-flight training #1
1620	PAB
1650	ZITA
1720	EEG hookup
1910	Dinner

The second day began with the collection of the resting (eyes-closed/eyes-open) EEG, the early-component ERP and the P300 ERP data. A session of PAB and ZITA was followed by the second training flight. In-house training was again administered (EEG, ERP, PAB, and ZITA), followed by the third training flight (Table 3). Thus, at the conclusion of the second day, each subject had received three training flights, four training sessions on the PAB and ZITA, and two training sessions on the EEG and ERP tasks. If, after the third training flight, a computerized flight evaluation (based on AIMS results) indicated the subject's flight performance had stabilized, the next day became the first dose

Table 3.

Activity schedule for atropine study, phase II. Training day.

```

=====
0600    Wake up
0630    Breakfast
0700    EEG electrode repair
0720    ERP
0810    PAB
0840    ZITA
0920    Helicopter systems check
0930    Helicopter in-flight training
1200    ERP
1250    PAB
1320    ZITA
1350    Lunch
1445    Helicopter systems check
1455    Helicopter in-flight training
1710    Dinner
=====

```

day. If, however, the subject needed more flight training, one or two more training sessions (an additional day) could be used to stabilize flight performance⁴.

⁴Due to the amount of time required for computer analysis of flight training data, if the third or fourth flight took place on the morning of the 3rd day, we generally proceeded with the afternoon in-house training session while awaiting the decision. Thus, 3 of the 12 subjects received an extra in-house training session above what would have been expected based upon the number of flight training sessions.

After training was complete (flight performance stabilized), the actual atropine testing began. Testing consisted of three dose-administration days, each of which was separated by a single control day on which no flights were made, and only laboratory tests were conducted. On each dose-administration day, only one injection (either placebo or 2 mg or 4 mg of atropine) was administered i.m. into the right thigh. Each subject received all three injections according to a randomly assigned, counter-balanced dose-administration order (Table 4). So a preliminary analysis could be based on a balanced set of dose orders, the subject pool was divided in half (subjects 1-6 were in group 1; subjects 7-12 in group 2). The six orders were randomly assigned among the subjects in each group. Neither the subjects nor the

Table 4.

Dose administration sequence.

```

=====
Subject          Test day
                1          2          3
-----
  1      placebo    4 mg     2 mg
  2      placebo    2 mg     4 mg
  3        4 mg     placebo   2 mg
  4        2 mg     4 mg     placebo
  5        2 mg     placebo   4 mg
  6        4 mg     2 mg     placebo
  7        4 mg     2 mg     placebo
  9        4 mg     placebo   2 mg
 10      placebo    2 mg     4 mg
 11      placebo    4 mg     2 mg
 12        2 mg     placebo   4 mg
 13        2 mg     4 mg     placebo
=====

```

researchers, with the exception of the principal investigator, were aware of which dose-administration sequence was used.

A dose-administration (or test) day consisted of three in-house testing sessions interspersed with two helicopter flights. Each of these days began with an EEG electrode check and repair followed by placement of ECG electrodes and insertion of the rectal probe used to monitor body temperature (although some subjects preferred to delay probe insertion until immediately prior to the first flight). Afterwards, the in-house (laboratory) testing began. This testing always occurred in the

same order, with vision tests being administered first, EEG/ERP data collected second, PAB being administered third, and the ZITA administered fourth (Table 5).

Table 5.

Activity schedule for atropine study, phase II. Test day.

```
=====
0500    Wake up
0530    EEG electrode repair, ECG hookup,
        and core body temperature probe
0630    Breakfast
0700    Visual battery
0720    ERP
0810    PAB
0840    ZITA
0920    BP, pulse, and temperature check;
        telemetry hookup
0935    Helicopter system check
0945    ** DOSE **
0950    Helicopter in-flight testing
1200    BP, pulse, and temperature check
1210    Visual battery
1230    ERP
1320    PAB
1350    ZITA
1410    Lunch
1445    BP, pulse, and temperature;
        telemetry check
1500    Helicopter systems check
1510    Helicopter in-flight testing
1720    BP, pulse, and temperature check
1740    Visual battery
1800    ERP
1850    PAB
1920    ZITA
2000    Dinner
=====
```

At the conclusion of the ZITA task, physiological monitoring sensors were checked, the subject was escorted to the aircraft, and the proper connections for EEG telemetry, ECG monitoring, and rectal temperature monitoring were established and verified. Once it was determined all subsystems were fully operational, the dose was administered (in the morning only), and the in-flight

testing began. The sequence of in-flight maneuvers was constant across all flights (see Table 6).

Table 6.

Precision in-flight maneuvering profile.

Hdg (deg)	Alt (ft)	A/S (kts)	Maneuver	Time from dose	
				a.m.	p.m.
180	1000	90	Standard rate 360° right turn	00:14	05:38
180	1000	90	Straight-and-level no. 1 (2 min)	00:17	05:41
180	1000	90	Standard rate 360° left turn	00:20	05:44
180	1000	90	Straight-and-level no. 2 (2 min)	00:23	05:47
270	1000	90	Climb 500 feet per min to 2000'	00:27	05:51
270	2000	90	30° bank left turn 720°	00:31	05:55
270	2000	90	Straight-and-level no. 3 (2 min)	00:35	05:58
270	2000	90	30° bank right turn 900°	00:38	06:02
090	2000	90	Straight-and-level no. 4 (2 min)	00:42	06:06
090	2000	90	360° standard rate descending right turn to 1000'	00:45	06:10
090	1000	90	Straight-and-level no. 5 (2 min)	00:49	06:13
090	1000	90	360° standard rate climbing left turn to 2000'	00:52	06:16
na	2000	90	Descend 500 feet per min to 1000'	00:57	06:20
na	na	na	Confined area reconnoiter and approach		
na	na	na	Out-of-ground-effect hover		
na	na	na	Low-level navigation		
na	na	na	Nap-of-the-earth navigation		
na	na	na	Vertical helicopter IFR recovery procedure		
na	2000	90	Straight-and-level no. 6 (2 min)	01:52	07:11
060	2000	90	ILS approach	02:03	07:26

While the subject was completing the morning in-flight evaluation, the schedule for the remainder of the day was adjusted to ensure the elapsed time from dose at which each subsequent task was administered remained the same across subjects regardless of any fluctuations in the actual time of dose administration. Upon completion of the in-flight testing, the subject performed another set of in-house testing, followed by lunch, and the second in-flight evaluation. At the conclusion of the second flight, the subject completed another in-house

evaluation after which he was free to retire for the evening. Thus, each dose-administration day consisted of three in-house sessions (one of which occurred before atropine administration) and two in-flight evaluations.

The control days which followed each dose-administration day were used primarily to ensure all atropine effects had subsided prior to the next dose. On these days, two complete in-house testing sessions were administered, but no atropine was given and no in-flight testing was conducted (Table 7).

Table 7.

Activity schedule for atropine study, phase II. Control day.

```
=====
0600    Wake up
0620    EEG electrode repair
0700    Breakfast
0730    Visual battery
0750    ERP
0840    PAB
0910    ZITA
0945    Biographical and smoking questionnaires
        (first day only)
1100    Lunch
1145    Visual battery
1205    ERP
1255    PAB
1325    ZITA
=====
```

Physiological data collection

On the morning of each dose-administration day, each subject was provided ample physiological monitoring to ensure his safety while in flight. Because of the effects of atropine upon heart rate and sweat production, both the ECG and core body temperature were monitored continuously during each flight. If the number of heart beats per minute (bpm) exceeded 150 for 15 minutes or if the core temperature exceeded 38.5°C (101.3°F), the flight was terminated.

Six ECG electrodes were applied to the subject's chest and side after each site had been properly shaved, cleaned, and abraded. Then the subject was given thorough instructions on the manner in which to insert the rectal probe, provided with the

probe and necessary supplies, and directed to accomplish this task himself.

In-flight performance evaluation

A safety pilot⁵ flying in the left seat of the research aircraft graded each subject's performance on certain maneuvers against standards established by the Aircrew Training Manual (Department of the Army, 1984). The grades consisted of scores ranging from 1 to 5, each associated with a particular level of flight performance accuracy (performance band). The bands were established around the ATM standards for each maneuver with a score of 3 being the standard for the performance measure in that maneuver. Scores higher than three represented performance which exceeded the minimum acceptable performance level and those below three represented substandard performance. An overall performance score for each maneuver was computed by averaging the scores of each measure within a maneuver.

In addition to these safety pilot grades, each subject's flight performance also was evaluated with the onboard computerized monitoring system described earlier. The only time both systems were not employed concurrently was during maneuvers which were not amenable to computer scoring (such as confined area operations).

The flight profile required the aviator to perform a measurable aviation task at all times during each of the flights (approximately 2:10). The entire profile was assembled to permit the measurement of aviator performance during operationally relevant flight tasks, but paced so the safety-pilot could intervene if required. Subjects were trained on the upper-air work and the confined-area maneuvers; but, no training was given on the navigation portion of the profile. Dosage for the day was administered while the subject was seated in the aircraft, immediately prior to the morning flight. None of the parties involved knew the amount of atropine in the injection.

Each subject began by flying a series of upper-air maneuvers sharing some commonality with more complex helicopter maneuvering tasks such as air-to-air combat, low-level flight, and nap-of-the-earth (NOE) flight (Figure 3). The aviators then moved on to

⁵The same safety pilot/performance rater flew all missions during this study. Chief Warrant Officer D. J. Carter had 6,300 hours pilot experience over a period of 20 years. He had been an instructor pilot for 18 years with a total of 2,950 hours. As with the rest of the experimental personnel, he was not informed of the dose levels.



Figure 3. JUH-1H helicopter at nap-of-the-earth altitude.

the next portion of the flight profile which simulated a common tactical mission of ingress into a forward battle position. Here, the pilots were to reconnoiter and land in a confined area. While in the confined area, they were to perform an out-of-ground-effect hover maneuver.

Upon completion of these flight tasks, the safety pilot flew the aircraft. Subjects were given a tactical map marked with both low-level and NOE navigation courses. The courses, new to the subjects now serving as navigator/copilot, called for them to navigate up to 65 kilometers low-level and 30 kilometers NOE. The navigation exercise required regular continued cognitive effort to decipher map symbology into meaningful representations of the physical world. Low-level navigation--involving decision-making, route planning, and giving directions to the pilot--requires continuous split-second decisions while moving at a speed of approximately 100 mph at only 200 feet above the surface of the earth. Thus, the inclusion of this exercise required continuous cognitive processing.

The final phase of the profile, with the subject at the controls again, tested the pilot's ability to operate the aircraft after the majority of his visual cues were removed.

While at NOE altitude, the subject was instructed to affix a hood to his helmet which restricted his view of the earth and forced him to fly using only the flight instruments (Figure 4). He then was directed to perform an immediate climb to altitude to simulate inadvertent flight into low-lying clouds after which he flew the last straight-and-level segment. The profile ended with a precision ILS approach to landing.

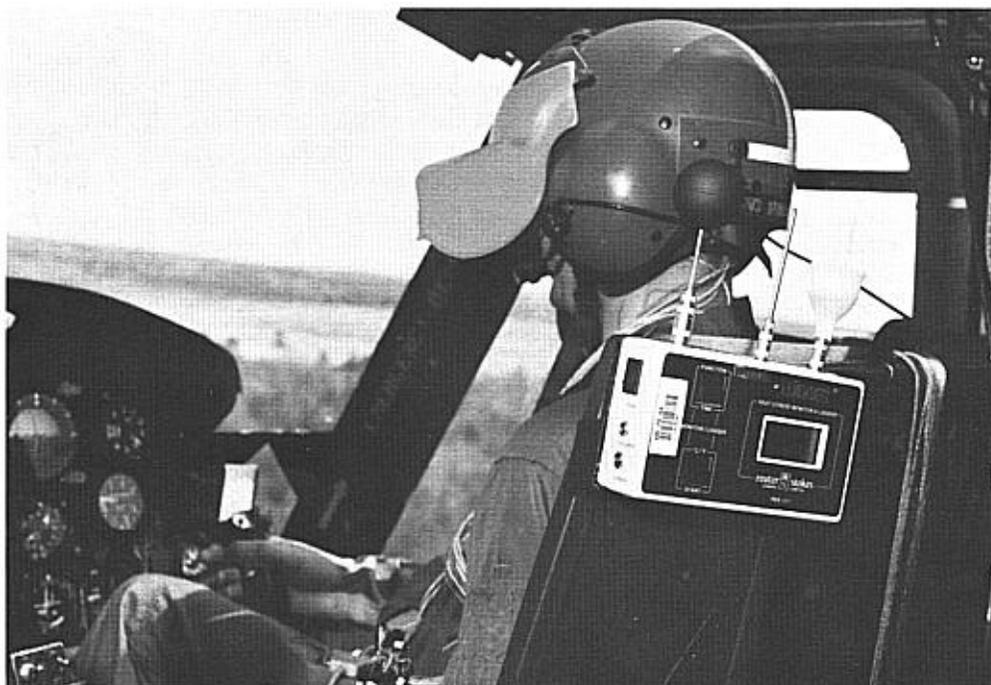


Figure 4. Subject pilot wearing visibility-restricting hood.

All maneuvers within the profile were flown in the same order across all trials. The profile was arranged so the maneuvers increased in difficulty throughout the flight.

Vision tests

Since it was deemed unnecessary to "train" subjects on taking vision measurements, all vision tests were explained fully to each subject during the testing procedure on the morning of the first dose-administration day rather than being included as part of the training-day schedule. Subjects generally were given all of the tests in the same order across all conditions; however, the order was modified slightly on a few occasions. The primary test sequence began with autorefraction, proceeded through the measurement of heterophoria, accommodation, near

point of convergence, pupil diameter, near visual acuity, stereopsis, fusion, near contrast sensitivity, and ended with assessments of both distant visual acuity and distant contrast sensitivity. Subjects were exposed to the complete set of vision tests three times on each dose-administration day (morning, noon, and evening) and two times on each control day (morning and noon).

Electroencephalographic electrode hookup

At the end of the first training day, each subject was seated in a comfortable chair and thoroughly briefed concerning the procedure to be used for electrode attachment. Twenty-five electrodes were attached to the subject's scalp using collodion. In addition to all of the standard placement sites delineated in the International 10/20 system, electrodes were placed at Fp_2 , O_2 , below O_2 (isoground), and on both left and right mastoid processes (A_1 and A_2). All sites were initially located using prescribed measurement procedures, marked with a grease pencil, and then cleaned with acetone. After suitable preparation of each site, electrodes were attached and filled with conductive electrolyte gel. Then, all 25 leads were connected to the interface and the subject was allowed to retire for the evening.

Impedances were checked for the first time on the morning of the second training day after all electrodes were re-gelled. In the event of impedance readings in excess of 5000 Ohms, slight abrasion of the site was accomplished by gently rotating a blunted needle within the problem electrode until the impedance dropped to an acceptable level. Additionally, any electrodes which had fallen off during the night were reattached at this time. From this day forward, each day (training, dose-administration, or control) began and ended with electrode check and repair. Subjects wore all 25 EEG electrodes throughout the entire testing period (a minimum of 8 days).

Electroencephalographic testing

A number of EEG measures were collected on each subject to assess the effects of atropine on CNS functioning. Each EEG test session began with an examination of general activation level, proceeded through a test of the speed with which certain visual stimuli were "registered" by the brain, and ended with a task which provided some indication of how each subject's cognitive processing, reflected in the P300, was being affected. All subjects completed at least two training-day sessions on the EEG/ERP testing procedures. Occasionally, subjects would require some instruction regarding their need to minimize eye movements or reduce the level of muscle tension so relatively artifact-free

signals could be obtained. Generally, these minimal training sessions were sufficient to resolve any problems.

Each EEG/ERP testing session consisted of the same tests administered in the same order. Subjects were escorted to the testing chamber, seated in a comfortable chair, and instructed to minimize any type of body movement or eye movement. All 21 active channels were referenced to linked mastoids and grounded to the isoground located below O_2 . For the resting EEG, the subject was instructed to first look straight ahead while keeping his eyes-opened until he heard a knock on the door (approximately 60 seconds into the task). After hearing the knock, the subject was to continue holding his eyes straight ahead while keeping them closed until the end of the test (another 60 seconds). Thus, 60 seconds of data were collected for each condition in the resting EEG.

After the resting EEG, the experimenter returned to the testing chamber and explained to the subject he would be exposed to a series of common black-and-white checkerboard pattern reversals presented on the CRT. For this early-component ERP test, he was expected to sit quietly, minimize eye movements, and simply observe the pattern reversals in a passive manner while ERP data were collected. The subject's chair then was situated so the CRT was approximately 1 meter from the bridge of the subject's nose. After the experimenter left the booth, the first set of checkerboards was presented. Following a total of 100 half-second collection sweeps in response to reversals presented at a rate of 3.90 repetitions per second, the experimenter reentered the chamber and chatted informally with the subject while the next task was prepared. This procedure was repeated until evoked responses had been gathered for all six checkerboard patterns ranging from very large checks to very small checks (4 squares x 4 squares, 8x8, 16x16, 32x32, 64x64, and 128x128).

Following the early-component evoked response testing, the subject was connected to the Cadwell 7400 and a single channel of evoked responses was collected for the P300 task. The leads consisted of P_z referenced to A_z and grounded to F_z . The subject was instructed to again watch the monitor; but, rather than sitting passively, he was to press a hand-held pushbutton every time a pattern reversal occurred. Then, a 4x8 checkerboard pattern was presented; and, this pattern reversed a total of 26 times out of 200 three-quarter-second data collection sweeps.

Preamplifier settings for the Spectrum 32 during the resting EEG testing were: sensitivity of 5.0, high cut filter at 100 Hz, time constant set at 0.30. The 60 Hz notch filter was used. Settings for the Spectrum during the early component ERP were: gain of 20, high cut filter at 100 Hz, low cut filter at 1.0 Hz, and the 60 Hz notch filter engaged. The Cadwell 7400 settings

used during the P300 task were identical to those used on the Spectrum during the early component ERP.

All three components of the EEG/ERP testing were administered three times per day (morning, noon, and evening) on dose-administration days and two times per day (morning and noon) on control days. Identical procedures were used each time the tests were given.

Performance assessment battery

All subjects completed at least four training sessions on the PAB, with the possibility of more if the subject required extra flight training. Since training on the laboratory tests was keyed to the flight training schedule, subjects were not necessarily trained to the point of stable performance on the PAB. During the first training session, each subject was familiarized with the purpose of PAB testing, the apparatus to be used, and the requirements of the battery. Subjects were instructed to emphasize both speed and accuracy in the performance of each subtest. Initially, subjects were encouraged to ask for help at any point during test administration, but as training progressed, the subject was required to function with increasing autonomy until, by the fourth session, each subject was encouraged to take the tests exactly as he would on a dose day. The actual testing was conducted three times per day on each dose day (morning, noon, and evening) and two times per day on each control day (morning and noon). Feedback was available upon request after each session. The battery consisted of the following subtests presented in the same order each session beginning with the mood scale (not reported here) and ending with the four-choice reaction time (RT) test:

Mood-activation scale

Subjects were to rate on a 1-5 scale how a total of 65 individually presented adjectives reflected their current mood and activation. They were to press the numeric key corresponding to their choice.

Six-letter search

The subject was presented with a string of 6 letters at the top of the CRT screen and a string of 20 letters at the middle of the screen. He was to indicate by a simple true or false key press as quickly and as accurately as possible whether or not all letters from the first string were present in the second string.

Logical reasoning

The subject was presented with a letter pair "BA" or "AB," along with a statement describing a possible order of the two letters. He was to indicate by a simple true or false key press as quickly and as accurately as possible whether or not the statement was an accurate description of the displayed letter positions.

Digit recall

A string of nine digits was presented on the CRT for 1 second, followed by a 3-second blank screen, followed by a string of eight digits (in different order from the original string of nine). The subject was to indicate by a key press on the numeric keypad which of the digits presented in the first string was missing from the second string.

Serial addition/subtraction

Two single-digit numbers followed by either a plus sign or a minus sign were presented sequentially on the screen. The subject was to perform the indicated operation mentally and key in the answer. If the resultant answer was greater than or equal to 10, he was to subtract 10. If the answer was less than 0, he was to add 10. Thus, all responses ranged from 0 to 9.

Four-choice serial reaction time

The subject was given a hand-held stimulus/response panel equipped with four LEDs, arranged in a square, which were situated above four response keys arranged in the same pattern as the LEDs. He was to respond as quickly as possible to each LED stimulus by pressing the corresponding response key.

Zero input tracking analyzer

Fine motor coordination and ability to respond to concurrent tasking were measured using the zero input tracking analyzer (ZITA). In this series of tasks, a cursor presented on a dot matrix display remained constantly in motion (unless it reached the edge of the display). The subject was to use a joy stick to place the cursor as nearly as possible over a target in the center of the display and hold it there. The motion characteristics of the cursor changed from one level of difficulty to another depending upon the preselected program.

In task level 1, the velocity of the cursor remained constant and the cursor responded immediately to any reversal of the joy stick. In task level 2, the acceleration of the cursor remained constant. A joystick reversal decelerated the cursor at the same rate before reversing it. In task level 3, the acceleration of the cursor changed uniformly as the cursor moved (the change in velocity behaved differently from that seen in task 2). A reversal of the joystick caused the acceleration rate to decrease uniformly until reaching 0, then, it began increasing again with the cursor going in the opposite direction. As a result, there appeared to be a delay (of about 1 second) between a joystick reversal and a cursor response. In effect, tasks 2 and 3 could be characterized as being increasingly more difficult than task 1 because each level increased the effective delay from stick movement to cursor movement. The subject had to anticipate not only when to reverse the stick to have the cursor stopped over the target, but, in task 3, he also had to enter (before the cursor arrived at the target) the joystick manipulations to keep it there.

To further increase the demands of ZITA, the subject also was intermittently asked to perform a secondary auditory distraction task (ADT). He was to respond to randomly presented high and low tones by pressing one of two buttons (depending on whether the tone was high or low). The difficulty of the ADT was controlled by changing the number of tones presented per unit of time. At the lower difficulty level, the subject received one tone every 2 seconds (ADT2); whereas, at the higher difficulty level, the subject received one tone every second (ADT1). The runs without the ADT were dubbed ADT0.

Each subject initially was trained to operate the ZITA on the first training day using a procedure recommended by the ZITA's designer (Norman K. Walker Associates, Inc; n.d.). As with PAB, subjects were not necessarily trained to asymptote. The session consisted of a 14-trial interactive sequence with an experimenter. Immediately following the initial training session, the subject was given a preview of the nine-trial test sequence with the experimenter nearby in case of questions. The nine-trial test protocol included one run of each task at each level of ADT. The number of "preview" sessions varied depending upon the number of days needed for flight training of each subject, but was never less than four. For training and all subsequent sessions, the subject was seated at a table in a dimly lit testing booth where the ZITA console, a CRT, and a small switch were located. After the initial training, the subject initiated each run at his own pace by pressing the switch. A 5-second countdown following the switch press allowed him ample time to position his hand and prepare for the task. All subjects used their right hand to operate the joystick (just as they would use it to move the cyclic in the aircraft, regardless of their

handedness) and their left hand to respond to the auditory distraction task. At the conclusion of each run, the subject was presented with performance feedback along with parameters for the next run (presented on the CRT). Additionally, at the conclusion of each session, the subject was presented with a listing of all scores attained during the session.

Each testing session began with three task 2 runs (one for each level of auditory distraction), followed by three task 1 runs, and ended with three task 3 runs. Subjects operated tasks 2 and 3 for 60 seconds each and task 1 for 30 seconds⁶. Furthermore, there were three testing sessions on each dose-administration day (morning, noon, and evening) and two sessions per control day (morning and noon). All testing was conducted in the same order across all conditions, including "previews."

Results

Statistical procedures

All data were analyzed with BMDP4V, multivariate and univariate analysis of variance/analysis of covariance (Dixon et al., 1983) except as noted. Realizing subjects would continue to gain proficiency on each of the administered tasks as the experiment progressed, some correction for learning, practice, fatigue, and/or daily fluctuations in motivation was required. The chosen procedure was analysis of covariance using the pre-dose session of each dose-administration day as the covariate. This approach was felt to be the most useful of available strategies for providing the necessary adjustments required because of the extraneous influences listed above. However, we point out that the data may not have met all the assumptions desirable for analysis of covariance. First, there is apparently a great deal of uncertainty regarding the importance of parallel slopes in a within subjects design. We could not locate a procedure in either BMDP or SPSS-X which permitted a test for this assumption. Also, after consulting with other professionals and the published literature, we could not establish that this concern was even relevant here. So, the parallel slopes assumption may have been violated in some instances.

Second, when the effect of the covariate was nonsignificant, this did not result in the abandonment of the procedure. In consideration of the sheer multitude of dependent measures, the interpretive complexities, and the fact that learning/practice

⁶Task 1 calls for a rapid and persistent "jiggling" motion which quickly results in muscle fatigue.

effects were known to exist (whether significant or not when examining different measures within the same data set), we concluded the impact of violating this assumption (significant relationship between variate and covariate) was less of a problem than ignoring the subtle training/practice effects.

Thus, analysis of covariance was employed whenever possible (with the exception of the vision data), and the reported means in this document are adjusted means derived with BMDP2V. Of course, the flight data was not adjusted with this procedure because 1) subjects were trained to asymptote on the flight tasks, and 2) there was no predose flight on the dose-administration days.

Following the analyses of covariance or analyses of variance, significant interactions were followed up with analysis of simple effects to reduce the overall number of statistical comparisons. Once a determination was made regarding the factor level at which differences among cells occurred, the precise nature of these differences was ascertained with nonorthogonal contrasts. Note that because of the constraints of BMDP4V analysis of covariance procedure, calculations for session effects and interactions involving session were based on unadjusted scores. However, subsequent simple effects and contrasts were based on covariance-adjusted scores. Stringent corrections for alpha inflation were not instituted because we felt the increased probability of a type I error was acceptable in determining the safety rather than the efficacy of antidote use.

Because of the impact of sphericity assumption violations on the results obtained with repeated measures analyses, particular attention was paid to this assumption. Where appropriate, the Box/Geisser-Greenhouse corrected degrees of freedom (Grieve, 1984) were employed in calculating the probability levels associated with main effects and interactions. This correction was the most stringent one available. (The use of Box/Geisser-Greenhouse corrections generally results in fractional degree-of-freedom values.)

One final observation regarding data handling: All percentage values were first divided by 100 to yield a proportion, and then transformed with the $2 \cdot \arcsin(\sqrt{X})$ procedure recommended by Winer (1971). Some arcsin transformations of key percentage values are shown in Table 8. Although, our empirical assessment of the effects of this transformation indicated only small changes from what would have been obtained with raw percentages, the transformation was employed to stabilize the variances associated with this type of data.

Table 8.

Arcsin transformations of selected percentages after Winer (1971).

```

=====
% Transform      % Transform      % Transform
-----
10   0.6435      40   1.3694      70   1.9823
20   0.9273      50   1.5708      80   2.2143
30   1.1593      60   1.7722      90   2.4981
=====

```

Physiological data

Heart rates followed the expected atropine curve of initial short-term deceleration followed by a longer term acceleration. During the course of one subject's participation, one flight was terminated prematurely because his heart rate in the 4-mg condition exceeded the established limits (150 bpm for 15 minutes). Urinalysis findings indicated good hydration on all subjects during the course of participation.

In-flight performance

Objective measures

Computerized flight performance data were represented in RMS errors and percentage scores. Analyses of the results obtained with the two types of data indicated differences between the two were negligible. A canonical correlation indicated the dependency between the two sets of data could be adequately expressed using exactly nine canonical variables (there were nine original values or measures per set). Thus, there is little duplication across different measures (such as airspeed, altitude, and heading), which meant all were needed to describe the data adequately. In fact, Bartlett's (1941) test suggested every one of these variables was required ($p < 0.0001$). The strong relationship between the two types of scores (RMS and percent) was made more prominent by the high level of the smallest canonical correlation (0.75). The remaining correlations were between 0.87 and 0.99. Since the percentage scores were intuitively easier to interpret, only results based on analyses of these scores are reported here. The percentage scores contain information which is virtually identical to RMS errors, but they focus attention on the percentage of time subjects were

successful in accurately maintaining flight parameters to some optimal level rather than on the amount of error subjects were making.

The scores consisted of percentages which ranged from 0 percent (largest deviation) to 100 percent (almost perfect performance). They were computed by first categorizing each sample of a given measure (heading, airspeed, etc.) into one of 6 bins (0 percent, 20 percent, 40 percent, 60 percent, 80 percent, or 100 percent) depending upon how far that sample deviated from a predetermined standard as shown in Table 9. At the conclusion of this first step, each bin contained one integer value which represented the number of samples classified into that particular bin. Then, the number of total samples collected on each measure (i.e., airspeed, altitude, climb rate, etc.) during each maneuver was determined. The number of samples in each bin was multiplied by the weighting factor for the respective bin (0, 20, 40, 60, 80, 100); the results were summed and then divided by the total number of samples. Thus, at the completion of this entire procedure, there was one performance score (expressed as a percentage) per measure per maneuver. Prior to statistical analyses, these percentages were transformed using the arcsin transformation discussed earlier.

These scores, based on data collected with the AIMS, were analyzed using a series of repeated measures analyses of variance (ANOVA) in which maneuvers sharing common features were grouped. Of the many measures (i.e., airspeed, altitude, etc.) collected during each maneuver, only the relevant ones were analyzed for each particular maneuver. For instance, a measure of heading stability would be meaningless for turn maneuvers. Table 10 contains a listing of the flight maneuvers and the variables associated with each.

Before these analyses were undertaken, some data required estimation: one subject's morning flight on the 4-mg day was terminated prior to the seventh maneuver because of excessive heart rate (leaving maneuvers 7-15 missing); another subject's glideslope scores were missing during three flights because of a malfunction in the ILS at the approach airfield. The mean of the other subjects' scores on each of the missing variables was substituted using BMDPAM.

Straight-and-level maneuvers

There were six straight-and-level (SL) segments of the profile. The first five were identical; the final one was conducted under simulated instrument conditions. Because of this difference, the first five segments were analyzed together; the final one, SL 6, was analyzed separately. The three-way ANOVA (dose x

Table 9.
Scoring error bands.

<u>Variable</u>	<u>Band Limits</u>			<u>Units</u>
	0%	20%	40%	
Heading	12.000-999.000	6.000- 12.000	3.000- 6.000	Deg
Altitude	140.000-999.000	70.000-140.000	35.000- 70.000	Feet
Airspeed	16.000-999.000	8.000- 16.000	4.000- 8.000	Knots
Climb rate	800.000-999.000	400.000-800.000	200.000-400.000	Ft/min
Pitch	6.000-999.000	3.000- 6.000	1.500- 3.000	Deg
Roll	8.000-999.000	4.000- 8.000	2.000- 4.000	Deg
Slip ⁶	0.060-999.000	0.030- 0.060	0.015- 0.030	Gs
Localizer	3.800-999.000	1.900- 3.800	0.950- 1.950	Dots ⁷
Glideslope	3.800-999.000	1.900- 3.800	0.950- 1.950	Dots

<u>Variable</u>	<u>Band Limits</u>			<u>Units</u>
	60%	80%	100%	
Heading	1.500- 3.000	0.750- 1.500	0.000- 0.750	Deg
Altitude	17.500- 35.000	8.750- 17.500	0.000- 8.750	Feet
Airspeed	2.000- 4.000	1.000- 2.000	0.000- 1.000	Knots
Climb rate	100.000-200.000	50.000-100.000	0.000- 50.000	Ft/min
Pitch	0.750- 1.500	0.375- 0.750	0.000- 0.375	Deg
Roll	1.000- 2.000	0.500- 1.000	0.000- 0.500	Deg
Slip ⁶	0.008- 0.015	0.004- 0.008	0.000- 0.004	Gs
Localizer	0.475- 0.950	0.238- 0.475	0.000- 0.238	Dots ⁷
Glideslope	0.475- 0.950	0.238- 0.475	0.000- 0.238	Dots

⁷"Dots" are markings on the face of the glideslope indicator instrument by which the pilot estimates his position with respect to an ideal glide slope transmitted from a point at the end of the runway. A full deflection, or four dots, represents a flight path above or below a 0.7 degree envelope. Fractional readings are common.

Table 10.

Flight maneuvers and variables examined.

<u>Maneuver</u>	<u>Variables</u>
Straight-and-level	Altitude, airspeed, heading, vertical speed, pitch, roll, slip
Standard rate turn	Altitude, airspeed, rate of turn, rollout heading, vertical speed, pitch, roll, slip
Climb/descent	Airspeed, vertical speed, heading, level-off altitude, pitch, roll, slip
Steep turn	Altitude, airspeed, rate-of-turn, rollout heading, vertical speed, pitch, roll, slip
Climb/descent turn	Airspeed, vertical speed, rate of turn, level-off altitude, rollout heading, pitch, roll, slip
Confined area operations	Entry altitude, entry airspeed, approach angle, rate of closure, termination point
Hover (out-of-ground-effect)	Vertical ascent heading, altitude, position, vertical descent heading
Low level navigation	Location knowledge, identify checkpoints, final objective location
NOE navigation	Location knowledge, identify checkpoints, final objective location
Inadvertant IMC recovery	Heading, rate of climb, airspeed
ILS approach	Airspeed, localizer, glideslope, descent below decision height, vertical speed, pitch, roll, slip

Note: The list of variables is a combination of those scored by computer and/or safety pilot.

flight x SL) for SL 1-5 revealed a flight by maneuver interaction on altitude ($F(4,44)=3.07$, $p=0.0257$), airspeed ($F(4,44)=3.80$, $p=0.0097$), and vertical speed ($F(2.18,24.01)=10.19$, $p=0.0005$). Analysis of simple effects for the altitude interaction shown in Figure 5 indicated a maneuver effect during the afternoon (p.m.) flight ($F(4,44)=3.58$, $p=0.0130$) and a difference between the two

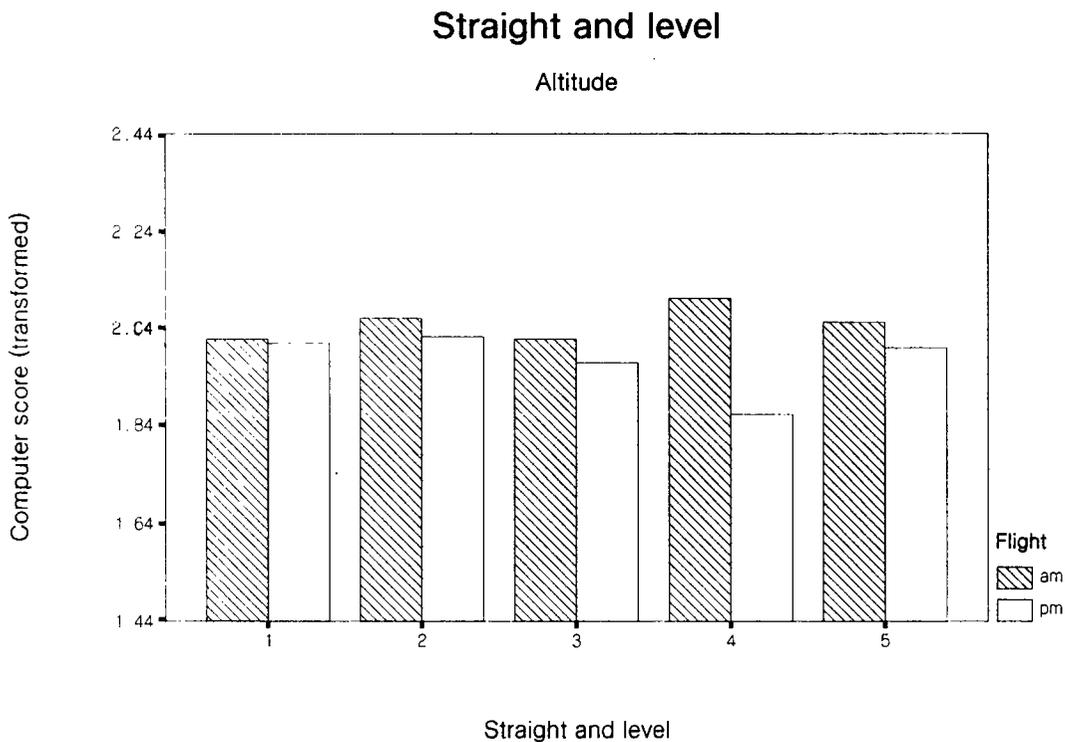


Figure 5. Flight by maneuver interaction for SLs 1-5 on altitude measure.

flights (a.m. better than p.m.) at SL 4 ($F(1,11)=2.52$, $p=0.0114$). Contrasts showed significant differences between SLs 1 and 4, SLs 2 and 4, and SLs 4 and 5 during the p.m. flight. These differences were attributable to a decrease in performance at SL 4 (Table 11).

Simple effects for the flight by maneuver interaction on the airspeed measure shown in Figure 6 indicated differences among maneuvers during the a.m. flight ($F(4,44)=2.52$, $p=0.0544$) and differences between the flights at SL 3 (a.m. better than p.m.) ($F(1,11)=5.74$, $p=0.0354$). Contrasts on the a.m. flights indicated significant differences between SLs 3 and 5 and SLs 4 and 5. A decrease in airspeed control at SL 5, relative to the other two, accounted for the difference (Table 12).

Analysis of simple effects for the flight by maneuver interaction on the vertical speed measure indicated differences among the various straight-and-level maneuvers at both a.m. ($F(4,44)=7.13$, $p=0.0002$) and p.m. ($F(4,44)=6.10$, $p=0.0036$), as can be seen in Figure 7 and Table 13. Contrasts on the a.m. flight revealed differences between SLs 1 and 5, SLs 2 and 3, SLs 2 and 5, SLs 3 and 5, and SLs 4 and 5. These differences occurred because of a performance improvement in SL 3 compared to

Table 11.

Contrasts for afternoon maneuver simple effect
for SLs 1-5 on altitude.

	Contrast	F	p
Maneuver in p.m.	SL 1 v 2	NS	
	SL 1 v 3	NS	
	SL 1 v 4	6.14	0.0307
	SL 1 v 5	NS	
	SL 2 v 3	NS	
	SL 2 v 4	8.09	0.0160
	SL 2 v 5	NS	
	SL 3 v 4	NS	
	SL 3 v 5	NS	
	SL 4 v 5	11.84	0.0055

Straight and level

Airspeed

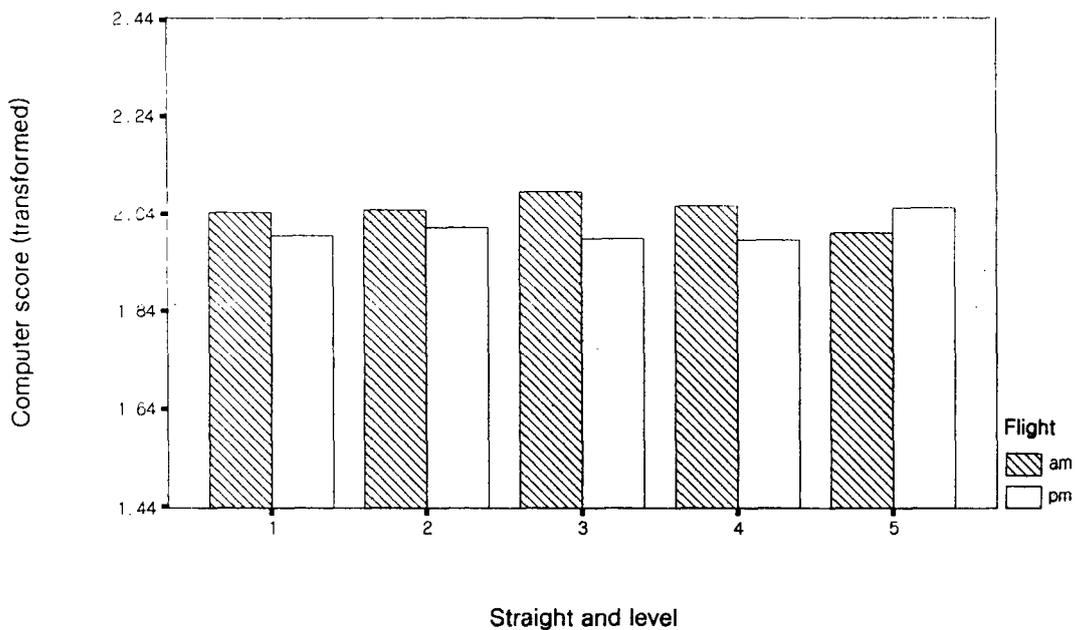


Figure 6. Flight by maneuver interaction for SLs 1-5 on airspeed measure.

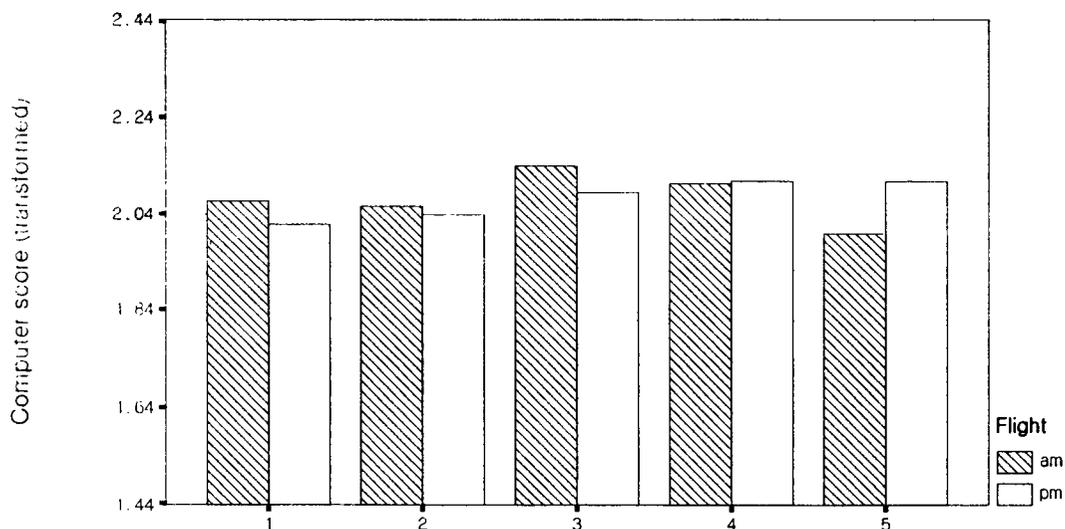
Table 12.

Contrasts for morning maneuver simple effect for SLs 1-5 on airspeed.

		Contrast	F	p
Maneuver in a.m.		SL 1 v 2	NS	
		SL 1 v 3	NS	
		SL 1 v 4	NS	
		SL 1 v 5	NS	
		SL 2 v 3	NS	
		SL 2 v 4	NS	
		SL 2 v 5	NS	
		SL 3 v 4	NS	
		SL 3 v 5	9.06	0.0119
		SL 4 v 5	9.73	0.0098

Straight and level

Vertical speed



Straight and level

Figure 7. Flight by maneuver interaction for SLs 1-5 on vertical speed measure.

Table 13.

Contrasts for maneuver simple effects in a.m. and p.m. for SLs 1-5 on vertical speed.

=====			
	Contrast	F	p

Maneuver in a.m.	SL 1 v 2		NS
	SL 1 v 3		NS
	SL 1 v 4		NS
	SL 1 v 5	4.76	0.0518
	SL 2 v 3	10.80	0.0072
	SL 2 v 4		NS
	SL 2 v 5	8.16	0.0156
	SL 3 v 4		NS
	SL 3 v 5	34.28	0.0001
	SL 4 v 5	22.89	0.0006

Maneuver in p.m.	SL 1 v 2		NS
	SL 1 v 3	6.54	0.0266
	SL 1 v 4	7.98	0.0165
	SL 1 v 5	11.38	0.0062
	SL 2 v 3	4.93	0.0484
	SL 2 v 4	8.32	0.0149
	SL 2 v 5	10.56	0.0077
	SL 3 v 4		NS
	SL 3 v 5		NS
	SL 4 v 5		NS
=====			

SLs 1 and 2, while there was a decline in SL 5 compared to SLs 1-4. Contrasts on the p.m. flight revealed no differences between the first two SLs (SLs 1 and 2) nor among the remaining three (SLs 3, 4, and 5). There was, however, a constant improvement in performance from the first to the fifth straight-and-level maneuver revealed in differences between the first two SLs and the last three SLs. Also, there was a flight effect at SL 5 ($F(1,11)=7.75$, $p=0.0178$) in which the p.m. flight performance was better than the a.m.

In addition to the flight by maneuver interaction, there was a main effect for maneuver on vertical speed ($F(2.14,23.50)=5.04$, $p=0.0136$) and pitch ($F(1.75,19.22)=7.92$, $p=0.0041$). Contrasts for the effect on vertical speed revealed differences between SLs 1 and 3, SLs 2 and 3, SLs 2 and 4, SLs 3 and 5, and SLs 4 and 5. Subsequent examination of the means showed a curvilinear relationship in which performance improved at SL 3 with respect

to SLs 2 and 1, and at SL 4 compared to SL 2; while performance decreased at SL 5 compared to SLs 3 and 4 (Table 14).

The maneuver effect on the pitch measure was different in that contrasts revealed differences between SLs 1 and 4, SLs 1 and 5, SLs 2 and 4, SLs 2 and 5, SLs 3 and 4, and SLs 3 and 5 which were simply a result of lower performance scores on the

Table 14.

Contrasts for maneuver effect for SLs 1-5.

=====			
	Contrast	F	p

Vertical speed	SL 1 v 2		NS
	SL 1 v 3	7.35	0.0202
	SL 1 v 4		NS
	SL 1 v 5		NS
	SL 2 v 3	15.16	0.0025
	SL 2 v 4	7.00	0.0228
	SL 2 v 5		NS
	SL 3 v 4		NS
	SL 3 v 5	11.64	0.0058
	SL 4 v 5	13.66	0.0035

Pitch	SL 1 v 2		NS
	SL 1 v 3		NS
	SL 1 v 4	11.06	0.0068
	SL 1 v 5	7.12	0.0218
	SL 2 v 3		NS
	SL 2 v 4	10.93	0.0070
	SL 2 v 5	6.26	0.0294
	SL 3 v 4	14.28	0.0031
	SL 3 v 5	11.61	0.0059
SL 4 v 5		NS	
=====			

latter maneuvers (SLs 4 and 5). This pitch change may have been at least partially due to changes in the aircraft center-of-gravity attributable to decreased fuel load as the 2-hour flight progressed.

Finally, there was a dose effect across all of the straight-and-level segments on heading precision ($F(2,22)=3.67$, $p=0.0421$). This effect was the result of a degradation in performance under

the 4-mg condition ($F(1,11)=5.93$, $p=0.0331$) as compared to the placebo condition (note the first column of Figure 8).

Computer scoring of flight performance

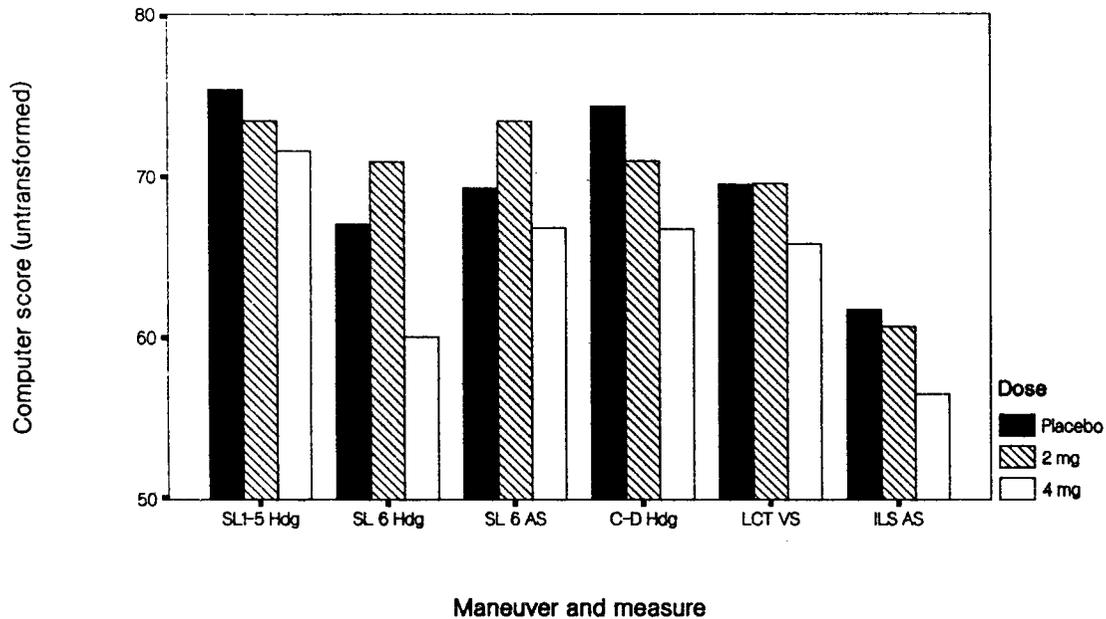


Figure 8. Computer scoring of flight performance.

As stated earlier, SL 6 (under simulated instrument conditions) was analyzed separately. The two-way ANOVA (dose x flight) for SL 6 revealed a dose by flight interaction on the altitude measure only ($F(2,22)=3.90$, $p=0.0354$). Simple effects indicated this interaction was due to a difference between flights under placebo ($F(1,11)=9.47$, $p=0.0105$) which was the result of improved performance during the p.m. flight (a similar tendency was probably suppressed by the 2- and 4-mg doses). There were similar findings with regard to flight differences on altitude ($F(1,11)=9.46$, $p=0.0105$), airspeed ($F(1,11)=36.20$, $p=0.0001$), vertical speed ($F(1,11)=43.86$, $p<0.0001$), pitch ($F(1,11)=5.23$, $p=0.0430$), and slip ($F(1,11)=11.51$, $p=0.0060$) which were revealed as significant flight effects. These effects were all due to better performance during the p.m. flight than during the a.m. flight.

Finally, there was a dose effect on both the heading measure ($F(2,22)=7.22$, $p=0.0039$) and the airspeed measure ($F(2,22)=8.54$, $p=0.0018$). For heading, performance declined in the 4-mg condition compared to both the 2-mg and placebo conditions

($F(1,11)=11.05$, $p=0.0068$ and $F(1,11)=5.10$, $p=0.0453$, respectively). For airspeed, performance declined in the placebo and 4-mg conditions compared to the 2-mg condition ($F(1,11)=4.76$, $p=0.0517$ and $F(1,11)=21.72$, $p=0.0007$, respectively). These effects can be seen in the second and third columns of Figure 8.

Standard-rate level turns

There were two standard-rate turn maneuvers in the profile. The first was a 360-degree right turn and the second was a 360-degree left turn. Since both turns followed the same parameters (with the exception of direction), they were analyzed together. The three-way ANOVA (dose x flight x maneuver) revealed a three-way interaction on vertical speed ($F(2,22)=3.90$, $p=0.0355$). Analysis of simple effects for this interaction indicated a maneuver effect (right turn better than left turn) under 4 mg during the a.m. flight ($F(1,11)=5.08$, $p=0.0456$) as seen in Figure 9. Also, there was a tendency toward a flight effect (a.m. better than p.m.) at 4 mg for the right turn ($p=0.0575$).

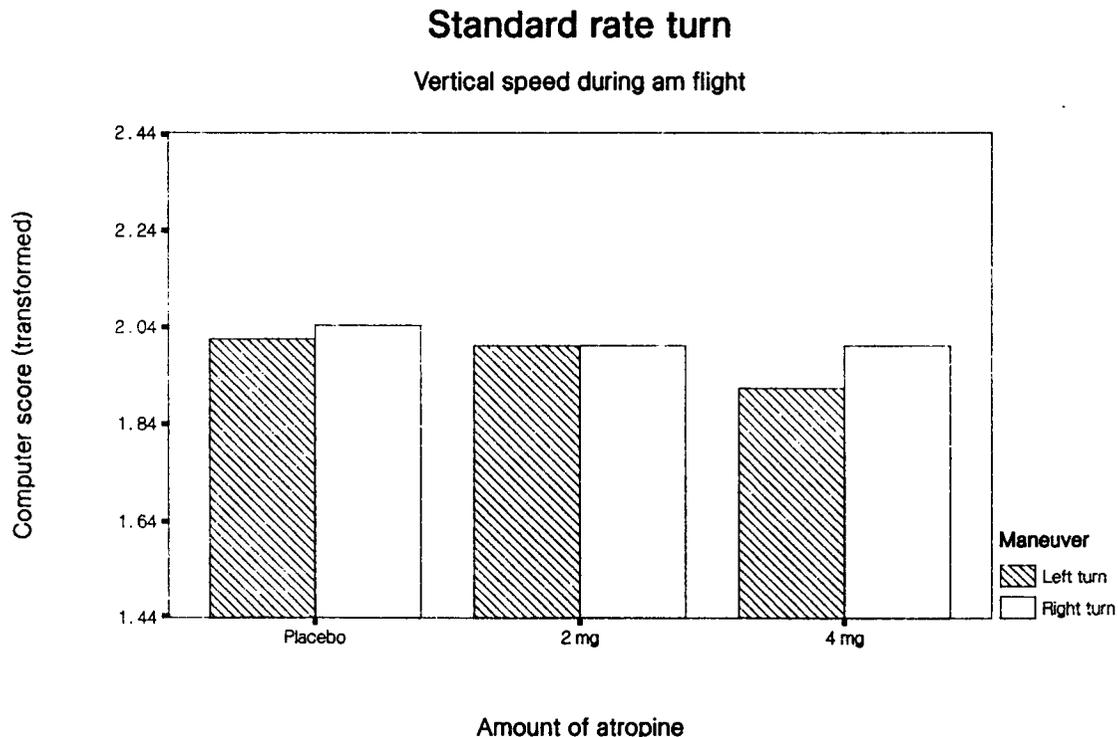


Figure 9. Dose by maneuver interaction for vertical speed in standard rate level turns during a.m. flight.

Additionally, there were flight by maneuver interactions for airspeed ($F(1,11)=4.81$, $p=0.0507$), vertical speed ($F(1,11)=4.92$, $p=0.0486$), and slip ($F(1,11)=13.58$, $p=0.0036$). Analysis of simple effects for these interactions revealed a difference between flights during the left turn on the airspeed measure ($F(1,11)=4.97$, $p=0.0476$) which resulted from reduced performance scores in the evening (Figure 10); a difference between maneuvers during the a.m. flight on vertical speed ($F(1,11)=5.64$, $p=0.0369$) which resulted from better performance scores on the right turn (Figure 11); and a difference between maneuvers in the morning ($F(1,11)=7.95$, $p=0.0167$) and flights at left turn ($F(1,11)=5.01$, $p=0.0468$) on the slip measure (Figure 12). These effects on slip resulted from lower performance scores for the left turn than for the right turn during the morning flight, and lower performance scores on the left turn in the morning than in the afternoon.

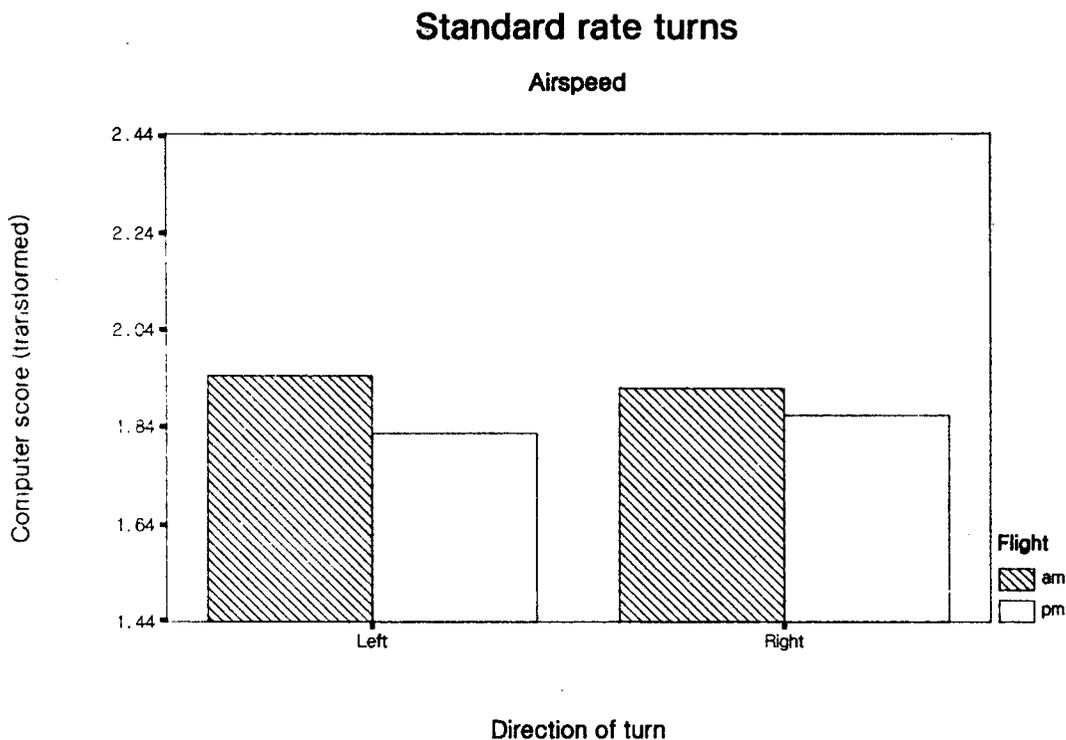


Figure 10. Flight by maneuver interaction for airspeed in standard rate level turns.

There was a dose by flight interaction involving the slip measure ($F(2,22)=3.75$, $p=0.0397$). Simple effects for this interaction revealed a difference between the two flights under the influence of placebo ($F(1,11)=5.82$, $p=0.0345$) which was apparently masked by the administration of either 2 or 4 mg of

Standard rate turns

Vertical speed

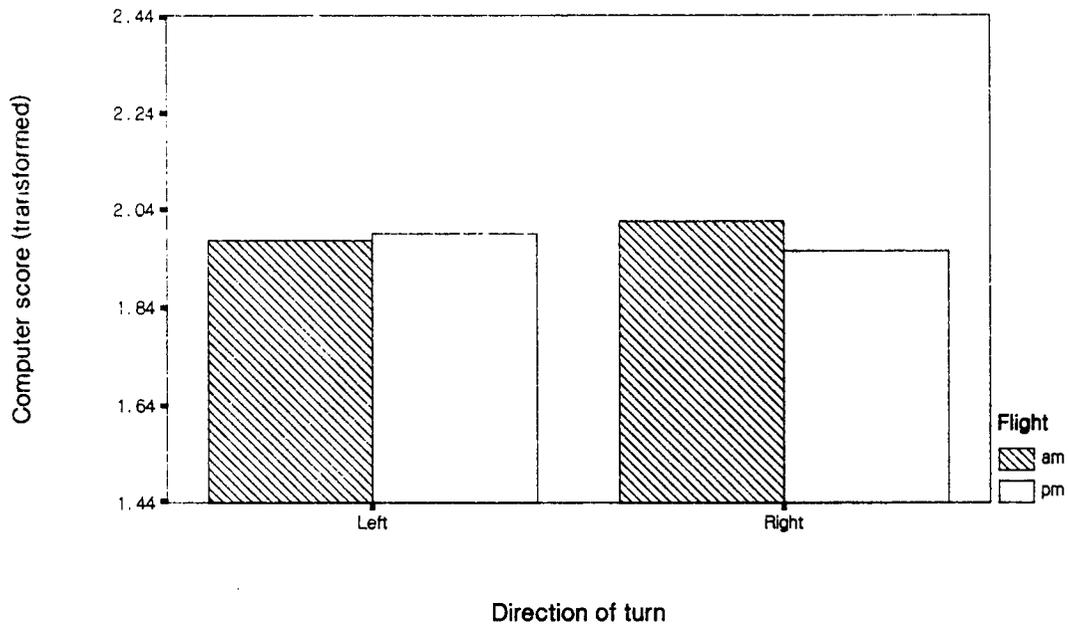


Figure 11. Flight by maneuver interaction for vertical speed in standard rate level turns.

Standard rate turns

Slip

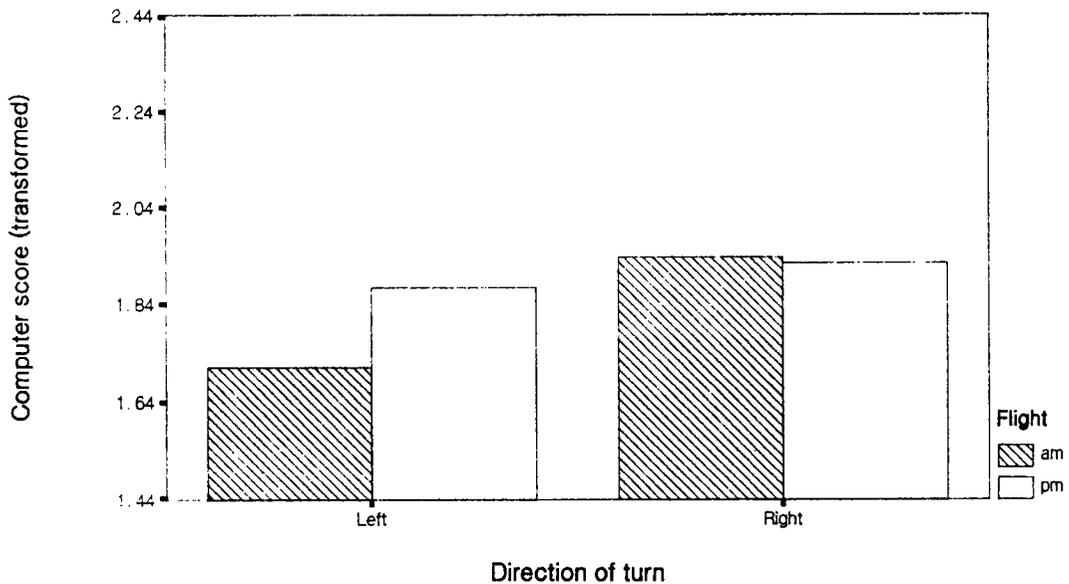


Figure 12. Flight by maneuver interaction for slip in standard rate level turns.

atropine (Figure 13). This effect was attributable to lower scores in the morning as compared to the evening under the placebo condition.

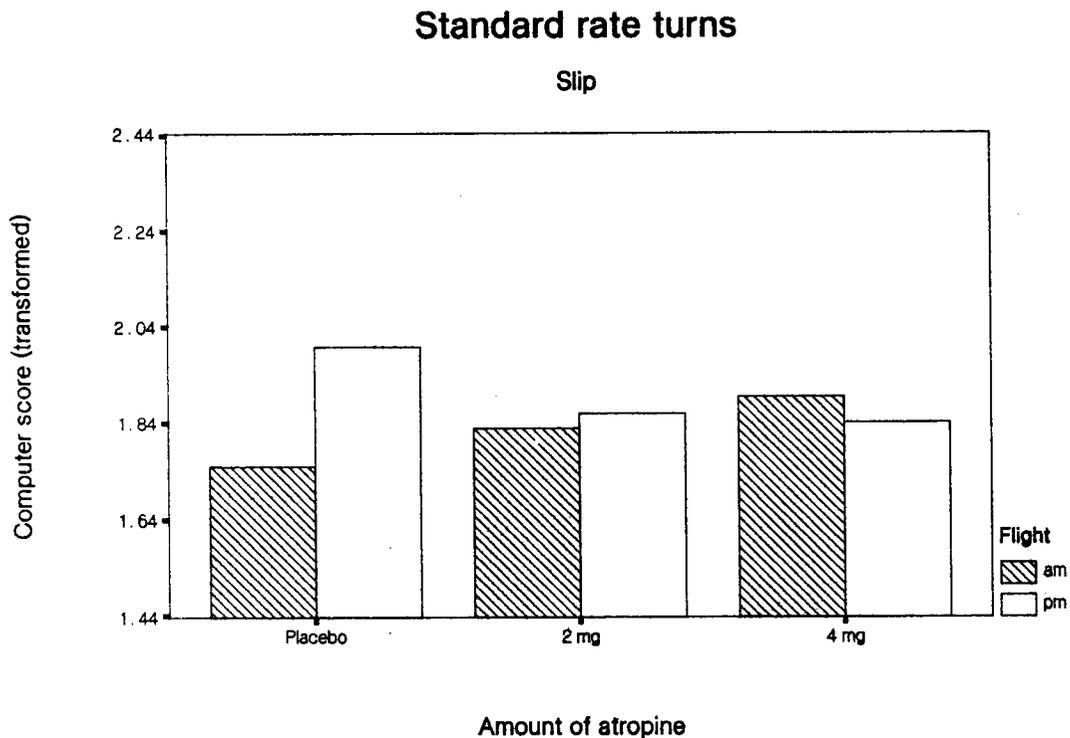


Figure 13. Dose by flight interaction for slip in standard rate level turns.

Finally, there was a maneuver effect on pitch ($F(1,11)=4.80$, $p=0.0510$) due to greater precision during the left turn than during the right turn, and a flight effect on the altitude measure ($F(1,11)=7.26$, $p=0.0209$) which resulted from a decrease in performance during the p.m. flights relative to the a.m. flights.

Straight climb and descent

There was one standard-rate (500 fpm) climb and one standard-rate descent which were analyzed together. The three-way ANOVA (dose x flight x maneuver) revealed a significant interaction among dose, flight, and maneuver for slip ($F(2,22)=4.18$, $p=0.0290$). Analysis of simple effects indicated a maneuver effect (descent better than climb) under 4 mg during the p.m. flight ($F(1,11)=9.32$, $p=0.0110$), a maneuver effect (descent better than climb) at placebo during the p.m. flight

($F(1,11)=5.40$, $p=0.0403$), a flight effect (p.m. better than a.m.) at placebo during the descent ($F(1,11)=11.41$, $p=0.0062$), and a dose effect at p.m. flight during the climb ($F(2,22)=3.35$, $p=0.0535$). These effects will be displayed in Figures 14, 15, and 16 as they are presented. Contrasts for the dose effect revealed a performance decrement under the 4-mg dose of atropine compared to 2-mg (Table 15).

Table 15.

Contrasts for dose X flight X maneuver interaction
for straight climb and descent.

```

=====

```

	Contrast	F	p
Dose in p.m.	0 mg-2 mg	NS	
for climb	0 mg-4 mg	NS	
(slip)	2 mg-4 mg	7.23	0.0211

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=====

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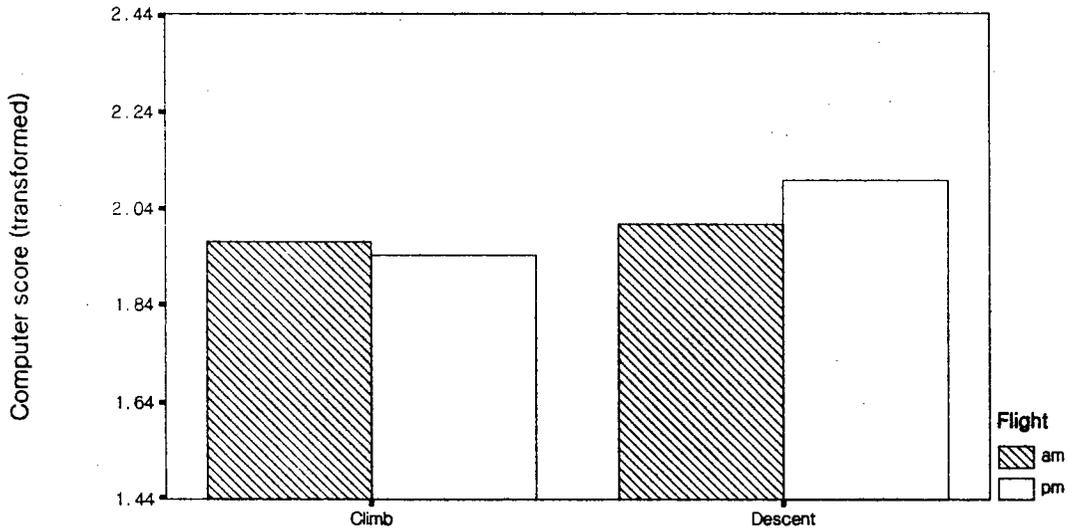
There was a flight by maneuver interaction for the airspeed ($F(1,11)=9.19$, $p=0.0114$) and the vertical speed ($F(1,11)=10.60$, $p=0.0077$) measures. Analyses of simple effects indicated there was a difference between the morning and afternoon flights during the descent, but not during the climb for both airspeed ($F(1,11)=6.31$, $p=0.0289$) and vertical speed ($F(1,11)=7.47$, $p=0.0197$). In both instances, the afternoon performance was better than morning performance (Figures 14 and 15).

Also, there was a maneuver effect for heading ($F(1,11)=10.94$, $p=0.0070$), airspeed ($F(1,11)=11.94$, $p=0.0054$), and pitch ($F(1,11)=5.06$, $p=0.0459$). Examination of the means for these three measures revealed subjects held the assigned heading and controlled their pitch better on the climb than on the descent; however, they maintained the assigned airspeed better on the descent than on the climb.

Finally, there was a dose effect on the heading measure ($F(2,22)=6.00$, $p=0.0083$) due to a significant performance decline between the placebo condition and the 4-mg atropine condition ($F(1,11)=7.23$, $p=0.0211$) as shown in the fourth column of Figure 8.

Straight climb and descent

Airspeed

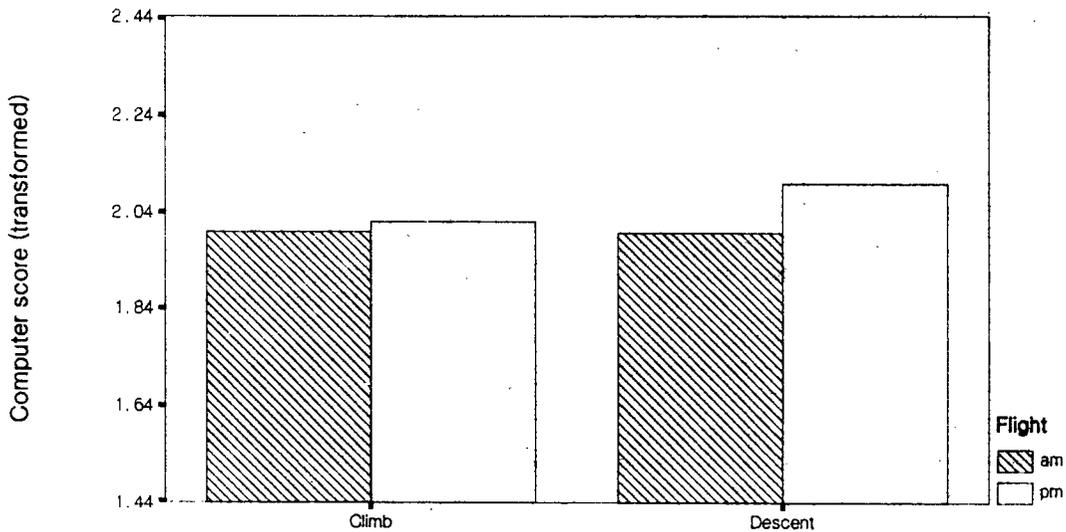


Maneuver

Figure 14. Maneuver by flight interaction for airspeed during straight climb and descent.

Straight climb and descent

Vertical speed



Maneuver

Figure 15. Maneuver by flight interaction for vertical speed during straight climb and descent.

Steep turns

Two 30-degree-of-bank steep turns were included in the profile. The first was a 720-degree (twice around) left turn and the second was a 900-degree (two-and-a-half times around) right turn which were analyzed together. The three-way ANOVA (dose x flight x turn) revealed a dose by flight interaction for the roll measure ($F(2,22)=3.57$, $p=0.0456$), found to be the result of a difference in performance between the morning and afternoon flights only under the 4-mg condition ($F(1,11)=16.07$, $p=0.0021$). Specifically, subjects evidenced more precise control of the angle of bank (roll) in the morning under 4 mg of atropine than in the afternoon under 4 mg of atropine (Figure 16).

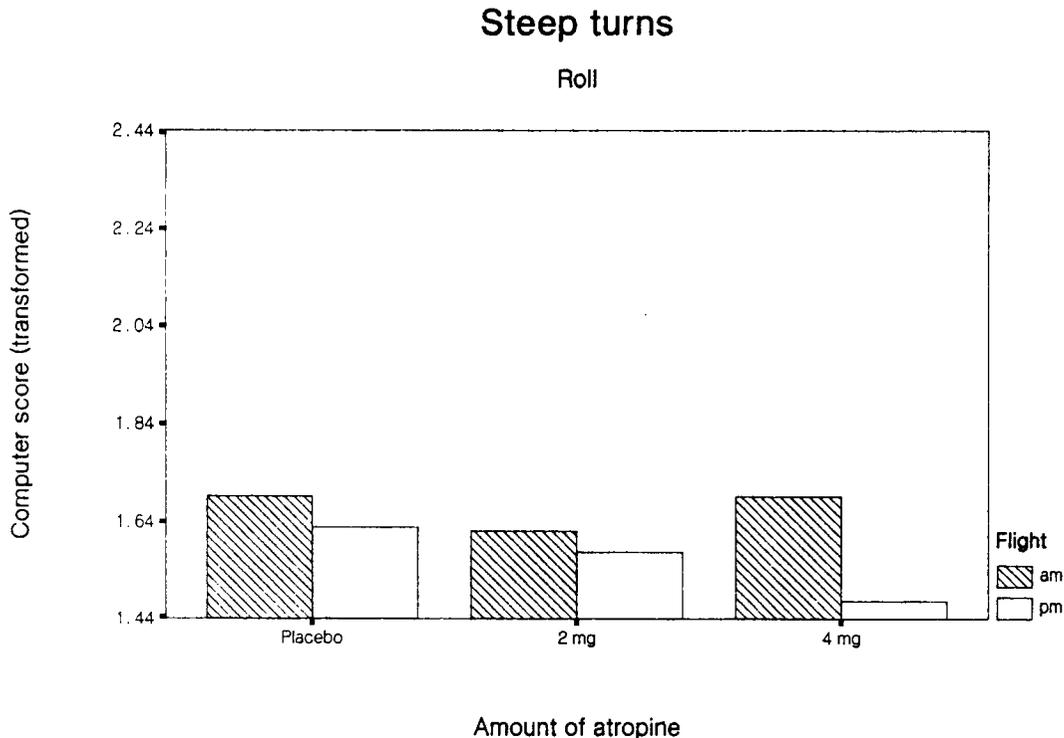


Figure 16. Dose by flight interaction for roll in steep turns.

Turn effects were found on two variables: the roll measure ($F(1,11)=8.66$, $p=0.0134$), and the slip measure ($F(1,11)=5.38$, $p=0.0405$). Subsequent examination of the means for these two measures on both turns revealed subjects maintained better control of roll and slip during the right turn than during the left turn.

Finally, there was a flight effect for roll ($F(1,11)=10.85$, $p=0.0072$) because performance on maintaining a specified roll angle was better overall in the morning than in the afternoon. There was not a main effect on the dose factor.

Standard-rate climbing and descending turns

A single 360-degree standard-rate descending right turn (15 degrees of bank at 500 fpm) and a single 360-degree standard-rate climbing left turn were included in the profile and subsequently analyzed together. The three-way ANOVA (dose x flight x maneuver) indicated there was a significant interaction between dose and maneuver on the vertical speed ($F(2,22)=4.85$, $p=0.0180$) and pitch ($F(2,22)=3.94$, $p=0.0344$) parameters. Analysis of simple effects revealed the interaction involving the vertical speed measure was attributable to a dose effect on the climbing turn ($F(1.52,16.76)=4.66$, $p=0.0324$), but not on the descending turn (Figure 17). Subsequent contrasts showed there was a significantly reduced performance under the 4-mg dose of atropine when compared to either the placebo ($F(1,11)=15.34$, $p=0.0024$) or the 2-mg ($F(1,11)=5.98$, $p=0.0325$) doses. This effect is depicted in the fifth column of Figure 8.

Climbing and descending turns

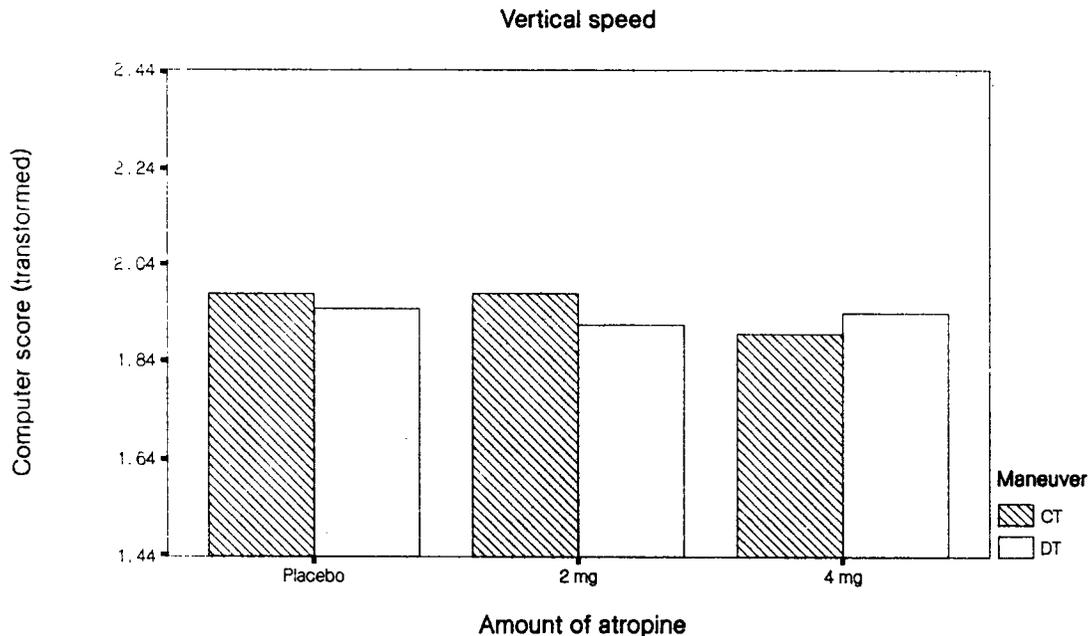


Figure 17. Dose by maneuver interaction for vertical speed during climbing and descending turns.

The interaction involving the pitch measure was not sufficiently large to produce any significant findings on the analysis of simple effects, although visual inspection of the six means suggested a tendency for performance on the climbing turn to have been better under the placebo and the 2-mg dose than under the 4-mg dose. During the descending turn, performance appeared to have been enhanced by the 4-mg dose relative to placebo, although the differences were not significant.

The ANOVA also revealed a maneuver effect on airspeed ($F(1,11)=19.47$, $p=0.0010$) and roll ($F(1,11)=5.38$, $p=0.0405$). Examination of the means involved in these interactions indicated performance was much better on the descending turn than on the climbing turn for both airspeed and roll measures.

Finally, some time-of-day effects were revealed by a significant main effect on the flight factor which involved the vertical speed measure ($F(1,11)=9.22$, $p=0.0113$). Inspection of the means for the two flights revealed performance was better during the afternoon flight than during the morning flight.

Instrument landing system (ILS) approach

The termination point of the profile consisted of an ILS approach into Cairns Army Airfield at Fort Rucker, Alabama. This maneuver was analyzed by itself in a two-way ANOVA (dose x flight). The analysis of variance revealed significant main effects for flight on airspeed ($F(1,11)=8.44$, $p=0.0143$), vertical speed ($F(1,11)=37.66$, $p=0.0001$), pitch ($F(1,11)=8.50$, $p=0.0141$), slip ($F(1,11)=6.17$, $p=0.0304$), and glideslope ($F(1,11)=5.54$, $p=0.0382$), all of which were due to improved performance during the afternoon flight in comparison to the morning flight.

Furthermore, there was a significant main effect for dose which involved the heading ($F(2,22)=5.08$, $p=0.0153$) and airspeed ($F(2,22)=6.10$, $p=0.0078$) measures. Contrasts for these effects indicated performance declined for heading in the 2-mg condition compared to the placebo condition ($F(1,11)=10.69$, $p=0.0075$), although this is probably meaningless since subjects were focused on the ILS localizer at this time. For the airspeed measure (Figure 8, sixth column), performance declined during the 4-mg condition when compared to both the placebo ($F(1,11)=11.81$, $p=0.0056$) and 2-mg conditions ($F(1,11)=7.67$, $p=0.0182$).

Subjective pilot grades

In addition to the computer scoring, the safety pilot onboard the research aircraft graded each subject's performance on the maneuvers against the standards published in the Aircrew

Training Manual (ATM) (Department of the Army, 1984). The grades consisted of scores ranging from 1 to 5 which were each associated with a particular bandwidth of deviation from prescribed flight performance ideals. The bands were established around the ATM standards for each maneuver with a score of 3 being the standard for the performance measure (heading, altitude, airspeed, etc.) in that maneuver. Scores higher than 3 represented performance which exceeded the minimum acceptable performance level, while scores below 3 represented substandard performance. An overall performance score for each maneuver was computed by averaging the scores of each measure within a maneuver.

These safety pilot grades were assembled on each of the maneuvers previously scored by computer and additionally on the confined area operations and the navigation segment. Portions of the third subject's 4-mg morning data again required estimation (preceding section). The grades on each scored parameter (Table 10 on p. 52) were analyzed in a fashion similar to the strategy used for the computer scores.

Straight-and-level maneuvers

The grades for each of the six straight-and-level (SL) segments of the flight profile were analyzed together using a three-way analysis of variance (dose x flight x SL) on three variables: altitude, airspeed, and heading. There were no three-way interactions, but there were some two-way interactions. For the altitude variable, there was an interaction between flight and SL ($F(2.60, 28.58) = 3.93, p = 0.0224$). Analysis of simple effects identified this interaction as due to an SL effect in the morning (SL 6 worse than SLs 1-5) ($F(5, 55) = 5.33, p = 0.0005$), and a flight effect only at SL 6, where a.m. was worse than p.m. ($F(1, 11) = 23.02, p = 0.0006$). Contrasts are listed in Table 16.

There was also a two-way interaction involving flight and SL for airspeed grades ($F(3.04, 33.49) = 6.29, p = 0.0016$). Analyses of simple effects identified an SL effect in both flights and a flight effect at SL 6. Contrasts among the SLs further located the principal source as only one maneuver (Table 17). There was a significant change of behavior on SL 6 during both flights, which is why this maneuver was later analyzed separately when examining computer scores of pilot performance (already discussed).

There were dose effects for both altitude and heading variables, and SL effects for the heading variable alone. The differences among SLs on the heading grades ($F(5, 55) = 3.02, p = 0.0176$) apparently were because performance on the third SL segment was much better than performance on the first, second, and sixth segments, and performance on the fourth SL segment was better than performance on the first (Table 18). Also, there was a

Table 16.

Contrasts for flight X SL interaction for subjective straight-and-level scores on altitude variable.

=====			
	Contrasts	F	p

	SL 1 v 6	18.22	0.0013
	SL 2 v 6	6.72	0.0250
	SL 3 v 6	8.41	0.0144
	SL 4 v 6	8.72	0.0132
	SL 5 v 6	8.22	0.0153
	SL 1 v 5		NS
	SL 2 v 5		NS
Altitude in a.m.	SL 3 v 5		NS
	SL 4 v 5		NS
	SL 1 v 4		NS
	SL 2 v 4		NS
	SL 3 v 4		NS
	SL 1 v 3		NS
	SL 2 v 3		NS
	SL 1 v 2		NS
=====			

decline in performance in the sixth SL compared to the fifth. The means for the heading grades are presented in Table 19.

Dose effects were found both on the altitude grades ($F(2,22)=6.09$, $p=0.0079$) and the heading grades ($F(2,22)=5.69$, $p=0.0102$). Subsequent examination of these sets of grades revealed poorer performance under the influence of the 4-mg dose than under the influence of placebo. In addition, on the altitude grades, the decline in the 4-mg condition compared to the 2-mg condition was significant (Table 20). Means are shown in Table 21.

Standard rate level turns

The 360-degree right turn and the 360-degree left turn were analyzed together in a three-way analysis of variance (dose x flight x turn). This analysis indicated there was an interaction between the dose and turn factors ($F(2,22)=4.68$, $p=0.0202$) involving rate-of-turn grades. Analysis of simple effects suggested this was attributable to dose effects observed in the left turn ($F(2,22)=4.91$, $p=0.0172$), which were absent in the right turn (see means at Table 22). Subsequent contrasts

Table 17.

Contrasts for flight X SL interaction for subjective straight-and-level scores on airspeed variable.

=====			
	Contrasts	F	p

	SL 1 v 6	6.96	0.0230
	SL 2 v 6	7.01	0.0227
	SL 3 v 6		NS
	SL 4 v 6	7.55	0.0190
	SL 5 v 6		NS
	SL 1 v 5		NS
	SL 2 v 5		NS
Airspeed in a.m.	SL 3 v 5		NS
	SL 4 v 5		NS
	SL 1 v 4		NS
	SL 2 v 4		NS
	SL 3 v 4		NS
	SL 1 v 3		NS
	SL 2 v 3		NS
	SL 1 v 2		NS

	SL 1 v 6	6.06	0.0316
	SL 2 v 6	5.21	0.0433
	SL 3 v 6	9.48	0.0105
	SL 4 v 6	16.50	0.0019
	SL 5 v 6	6.06	0.0316
	SL 1 v 5		NS
	SL 2 v 5		NS
Airspeed in p.m.	SL 3 v 5		NS
	SL 4 v 5		NS
	SL 1 v 4		NS
	SL 2 v 4		NS
	SL 3 v 4		NS
	SL 1 v 3		NS
	SL 2 v 3		NS
	SL 1 v 2		NS
=====			

revealed, within the left turn maneuver, there were significant decrements in subjects' control of turn rate as a function of both 2 mg and 4 mg atropine as compared to placebo (Table 23).

Table 18.

Contrasts for SL effect for straight-and-level maneuvers.

=====			
	Contrasts	F	p

	SL 1 v 2		NS
	SL 1 v 3	12.57	0.0046
	SL 1 v 4	4.66	NS 0.0538
	SL 1 v 5		NS
	SL 1 v 6		NS
Heading	SL 2 v 3	4.66	0.0538
	SL 2 v 4		NS
	SL 2 v 5		NS
	SL 2 v 6		NS
	SL 3 v 4		NS
	SL 3 v 5		NS
	SL 3 v 6	5.69	0.0362
	SL 4 v 5		NS
	SL 4 v 6		NS (0.0606)
	SL 5 v 6	5.02	0.0344
=====			

Table 19.

Mean safety pilot subjective ratings
for straight-and-level maneuvers.

=====	
SL	Heading

1	3.7083
2	3.7917
3	3.9167
4	3.9028
5	3.8447
6	3.6729
=====	

Table 20.

Contrasts for dose effects for straight-and-level maneuvers.

=====			
	Contrasts	F	p

Altitude	0 mg-2 mg		NS
	0 mg-4 mg	7.60	0.0187
	2 mg-4 mg	9.49	0.0105

Heading	0 mg-4 mg		NS
	0 mg-4 mg	10.36	0.0082
	2 mg-4 mg		NS
=====			

Table 21.

Mean safety pilot subjective ratings for dose effects.

=====				
Maneuver	Measure	Dose		
		0 mg	2 mg	4 mg

Straight-and-level	Altitude	3.8472	3.8403	3.6686
	Heading	3.8889	3.7917	3.7172

Standard-rate turn	Altitude	3.8125	3.6250	3.5625
	Airspeed	3.5417	3.4792	3.1458
	Roll-out heading	4.2292	4.0000	4.0208

Confined area	Airspeed	3.5833	3.6250	3.2992
	Approach angle	4.0417	3.6667	3.0946
	Rate of closure	4.0417	3.6250	3.2196

Out-of-ground effect (OGE) hover	Vertical-ascent heading	3.9167	3.6667	3.4888
	Hover altitude	4.0000	3.4167	3.2729
	Drift control	3.6250	2.7500	2.4888

Instrument landing system (ILS)	Airspeed	3.2083	2.7500	2.8562
=====				

Table 22.

Mean rate-of-turn scores for standard rate level turns.

Maneuver	Dose		
	0 mg	2 mg	4 mg
Right turn	3.9167	3.9167	3.8333
Left turn	4.0417	3.7917	3.6667

Table 23.

Contrasts for dose at left turn interaction for standard rate level turn.

	Contrasts	F	p
Left turn rate	0 mg-2 mg	6.60	0.0261
	0 mg-4 mg	7.24	0.0210
	2 mg-4 mg	NS	

Additionally, there were main effects on the dose factor on altitude grades ($F(2,22)=4.42$, $p=0.0243$), airspeed grades ($F(2,22)=6.69$, $p=0.0054$), and roll-out heading grades ($F(2,22)=8.66$, $p=0.0017$). The means are shown in Table 21. Contrasts conducted to pinpoint the nature of this effect showed the significance on the altitude grades was due to atropine-related performance decrements in both the 2-mg and 4-mg doses when compared to the placebo dose. The same basic pattern was apparent with roll-out heading grades. However, the contrasts done on the airspeed grades were partially inconsistent with those conducted on the other two variables since, even though there was poorer performance under 4 mg than under placebo, the decline between the placebo and 2-mg condition was not significant; whereas the decline in the 4-mg condition compared to the 2-mg condition was (Table 24).

Table 24.

Contrasts for dose effect for standard rate level turns.

=====			
	Contrasts	F	p

Altitude	0 mg-2 mg	6.06	0.0316
	0 mg-4 mg	7.33	0.0204
	2 mg-4 mg	NS	

Airspeed	0 mg-2 mg	NS	
	0 mg-4 mg	10.70	0.0074
	2 mg-4 mg	7.18	0.0214

Roll-out heading	0 mg-2 mg	12.44	0.0047
	0 mg-4 mg	9.48	0.0105
	2 mg-4 mg	NS	
=====			

Straight climb and descent

The grades on the standard-rate (500 fpm) climb and the standard-rate descent were analyzed in a single three-way analysis of variance (dose x flight x climb/descent) consistent with the strategy employed earlier with computer scores. The analysis indicated there was a significant three-way interaction among dose, flight, and climb/descent factors on the heading grades ($F(2,22)=12.59$, $p=0.0002$). Analysis of simple effects revealed, first, there was a dose by flight interaction at the climb maneuver ($F(2,22)=17.47$, $p<0.0001$), but not at the descent. Second, there was not a difference among the three doses during the morning flight at the climb maneuver, but there was a difference during the afternoon flight ($F(1.2,13.19)=12.29$, $p=0.0027$). Subsequent contrasts performed on data from the afternoon climb maneuver showed the significant dose effect stemmed from degradations in subjects' ability to accurately maintain an assigned heading in the 4-mg condition when compared to either the placebo or the 2-mg dose conditions (Table 25).

There was also an interaction between the dosage administered and the maneuver (climb or descent) on the grades for level-off altitude ($F(2,22)=4.19$, $p=0.0287$). Simple effects identified the source as the climb maneuver, since there was a dose effect at climb ($F(2,22)=5.08$, $p=0.0153$), but not at descent. Contrasts for the grades at climb indicated both doses of atropine caused performance decrements in comparison to placebo (Table 26).

Table 25.

Contrasts for dose effect within p.m. flight during climb.

=====			
	Contrasts	F	p

	0 mg-2 mg		NS
Heading	0 mg-4 mg	9.14	0.0016
	2 mg-4 mg	22.00	0.0007
=====			

Table 26.

Contrasts for dose at climb.

=====			
	Contrasts	F	p

	0 mg-2 mg	11.96	0.0054
Level-off	0 mg-4 mg	7.24	0.0210
altitude	2 mg-4 mg		NS
=====			

Two maneuver effects were found. These indicated performance on the climb was worse than performance on the descent with regard to maintaining precise airspeeds ($F(1,11)=8.72$, $p=0.0131$) and with regard to accurately leveling off at a prescribed altitude ($F(1,11)=5.67$, $p=0.0364$).

The effect of atropine, with other factors collapsed, was evident only in the heading grades ($F(2,22)=4.54$, $p=0.0224$). Contrasts revealed this effect was attributable to a significant reduction in performance in the 4-mg atropine condition as opposed to the placebo condition (Table 27). None of the other comparisons were significant.

Steep turns

The two 30-degree-of-bank steep turns, a 720-degree left turn and a 900-degree right turn, were analyzed together. The three-way ANOVA (dose x flight x turn) revealed no significant interactions and only two significant main effects. There was a significant effect on the turn factor ($F(1,11)=5.03$, $p=0.0465$) which was because of generally lower performance scores in

Table 27.

Contrasts for dose effect for climb/descent.

=====			
	Contrasts	F	p

	0 mg-2 mg		NS
Heading	0 mg-4 mg	9.93	0.0092
	2 mg-4 mg		NS
=====			

maintaining precise turn rate on the right turn in comparison to the left turn.

There was also a significant effect found on the dose factor ($F(2,22)=3.53$, $p=0.0468$). Subsequent inspection suggested this resulted from the tendency for subjects to score lower on holding a precise turn rate during the 4-mg dose than during the placebo ($p=0.0647$); however, none of the contrasts were significant.

Standard-rate climbing and descending turns

Safety pilot grades for the 15-degree-of-bank, 360-degree descending right turn and the 15-degree-of-bank, 360-degree climbing left turn were analyzed using one three-way ANOVA (dose x flight x climbing/descending turn). The analysis revealed an interaction between the dose factor and the maneuver factor (climbing/descending turn) on the airspeed parameter ($F(2,22)=7.44$, $p=0.0034$), which simple effects found was due to a dose effect for the climbing turn ($F(2,22)=8.02$, $p=0.0024$), but not for the descending turn. Contrasts on the airspeed grades at climbing turn showed performance was significantly worse under 4 mg of atropine than under either 2 mg of atropine or placebo (Table 28).

Table 28.

Contrasts for dose at climbing turn.

=====			
	Contrasts	F	p

	0 mg-2 mg		NS
Airspeed	0 mg-4 mg	13.72	0.0035
	2 mg-4 mg	13.27	0.0039
=====			

The only other effects revealed by this analysis were main effects of flight on both the airspeed grades ($F(1,11)=7.61$, $p=0.0186$) and the vertical speed grades ($F(1,11)=8.68$, $p=0.0133$). In both cases, performance was better in the afternoon than in the morning, as can be seen in Table 29.

Table 29.

Mean safety pilot subjective ratings for flight effects.

Maneuver	Measure	Flight	
		a.m.	p.m.
Standard-rate climbing/ descending turns	Airspeed	3.0114	3.3056
	Vertical speed	3.5251	3.7222

Confined area reconnoiter and approach

The straight descent to 1000 feet was followed immediately by the confined-area operations, in which subjects were graded on how well they held recon altitude and airspeed, how accurately they sustained a constant approach angle into the area, how well they maintained an acceptable rate of closure (speed of a "brisk walk") during the entry, and whether or not they terminated the entry in the forward part of the confined area as is the appropriate procedure. Only the safety pilot evaluated subjects during this part of the profile (there was no computer scoring of confined area operations). The safety pilot grades on each component of this segment of the profile were analyzed using a two-way analysis of variance (dose x flight).

Results of the analysis indicated dose effects on airspeed-control ($F(2,22)=5.45$, $p=0.0120$), approach-angle ($F(1.28,14.11)=7.97$, $p=0.0097$), and rate-of-closure ($F(1.27,14.02)=6.02$, $p=0.0220$). Contrasts revealed airspeed-control changes consisted of decrements in performance under 4 mg as compared to both 2 mg and placebo. The changes in both approach-angle control and rate-of-closure control consisted of degradations in performance under the 2-mg dose and the 4-mg dose as compared to placebo (Table 30). Means are shown in Table 21 on p. 72.

Table 30.

Contrasts for dose effect for confined area scores.

	Contrasts	F	p
Airspeed	0 mg-2 mg	NS	
	0 mg-4 mg	6.27	0.0293
	2 mg-4 mg	8.52	0.0139
Approach angle	0 mg-2 mg	7.24	0.0210
	0 mg-4 mg	15.31	0.0024
	2 mg-4 mg	NS	
Rate of close	0 mg-2 mg	11.96	0.0054
	0 mg-4 mg	9.62	0.0101
	2 mg-4 mg	NS	

Out-of-ground-effect hover

Before leaving the confined area and initiating the navigation portion of the flight profile, subjects performed a standard out-of-ground-effect hover to ensure the aircraft would be capable of making the rapid altitude changes necessary during low-level and NOE flight. Successful performance of this maneuver required subjects to ascend to an altitude of 50 feet (or one well above the highest obstacle) while maintaining a constant heading. Once reaching the hover altitude, subjects were graded on their ability to keep the aircraft from drifting in any direction while maintaining a stable hover altitude. After the aircraft hover check was complete, the subjects were to descend to the ground, exercising precise control over the aircraft heading. Performance on this portion of the flight profile was graded only by the safety pilot and not by the AIMS computer.

All of these grades were subjected to a two-way analysis of variance (dose x flight) which indicated there were no dose by flight interactions or flight main effects. However, there were dose effects on vertical-ascent heading grades ($F(2,22)=4.75$, $p=0.0193$), hover altitude grades ($F(2,22)=5.67$, $p=0.0103$), and drift-control grades ($F(2,22)=9.38$, $p=0.0011$). The mean grades are shown in Table 21 on p. 72. Contrasts revealed differences were attributable to degradations in performance under both the

2-mg and 4-mg conditions compared to the placebo condition (Table 31).

Inadvertent entry into instrument meteorological conditions (IMC)

Helicopter entry into "instrument conditions" forced the pilot to transition to instruments and begin climbing at a rate of 500 fpm. The inadvertent IMC was graded only by the safety pilot. The grades were analyzed in a two-way analysis of variance (dose x flight). There were no significant main effects or interactions.

Instrument landing system (ILS) approach

The instrument approach into Cairns Army Airfield at the end of the flight profile also was graded by the safety pilot. These grades were subsequently analyzed in a two-way analysis of variance (dose x flight) which revealed significant flight effects on the grades for glideslope ($F(1,11)=24.55$, $p=0.0004$) and for whether or not the subject descended below the minimum prescribed⁸ altitude ($F(1,11)=10.27$, $p=0.0084$). In both instances, the subjects performed better in the afternoon (3.9950 and 4.8333, respectively) than in the morning (3.2000 and 4.3131, respectively). There was also a dose effect on subjects' ability to maintain accurate airspeed control ($F(2,22)=3.66$, $p=0.0425$). Contrasts revealed performance was substantially worse under both 2 mg and 4 mg atropine than under placebo (Table 32). The means for this performance may be seen in Table 21 on p. 72.

Comparison of in-flight performance methods

The safety pilot ratings often were as sensitive to the effects of atropine as were the computerized measures. In some cases, the two sets of evaluations were quite similar and in others, they weren't. Differences and similarities between the two measurement schemes are discussed completely later.

⁸The "DoD Flight Information Publication (Terminal)" contains a chart of each runway to which a pilot may approach under instrument conditions. Each chart also shows the altitude below which the approaching aircraft may not be flown if the runway is not visible to the pilot a specified minimum distance ahead.

Table 31.

Contrasts for dose effect for out-of-ground-effect hover.

	Contrasts	F	p
Heading	0 mg-2 mg	6.60	0.0261
	0 mg-4 mg	7.28	0.0207
	2 mg-4 mg		NS
Hover altitude	0 mg-2 mg	5.67	0.0364
	0 mg-4 mg	11.71	0.0057
	2 mg-4 mg		NS
Drift	0 mg-2 mg	18.17	0.0013
	0 mg-4 mg	18.84	0.0012
	2 mg-4 mg		NS

Table 32.

Contrasts for dose effect for ILS approach.

	Contrasts	F	p
Airspeed	0 mg-2 mg	5.30	0.0418
	0 mg-4 mg	7.15	0.0216
	2 mg-4 mg		NS

Vision battery

The visual battery involved the administration of a series of standard diagnostic vision tests consisting of measures of pupil diameter, stereopsis, amplitude of accommodation, near point of convergence, gross visual fusion ability, near and far visual acuity, near and far static contrast sensitivity, and near

and far vertical and lateral phorias. Table 33 contains the means for all conditions.

Pupil diameter

Right and left pupil diameters for each of the 12 subjects were measured in millimeters during each of three sessions (a.m., noon, and p.m.) on each of the 3 dose days. These pupil diameter measures for the right and left eyes were submitted to separate 3 X 3 analyses of variance with repeated measures on each of the two factors (dose by session). Results of these analyses revealed dose by session interactions for both pupils ($F(4,44)=17.42$, $p<0.0001$ for the right pupil and $F(4,44)=17.85$, $p<0.0001$ for the left pupil). Analysis of simple effects for these interactions revealed session effects at 2 mg for both right and left pupil diameters ($F(2,22)=37.44$, $p<0.0001$ and $F(2,22)=47.73$, $p<0.0001$ respectively), and session effects at 4 mg ($F(2,22)=65.07$, $p<0.0001$ for both pupils). Furthermore, there were dose effects for both pupils at the noon session ($F(2,22)=23.12$, $p<0.0001$ for both pupils) and at the evening session ($F(2,22)=28.63$, $p<0.0001$ for the right pupil and $F(2,22)=30.31$, $p<0.0001$ for the left pupil) as depicted in Figure 18.

Contrasts for the session effects at 2 mg, shown in the top portion of Table 34, indicated the diameter of both right and left pupils increased from morning to noon. Pupil diameter under 2 mg also was larger during the evening session when compared to the morning session; however, there were no differences in pupil size between the noon and evening sessions for either eye. For the 4-mg dose of atropine, there were increases in pupil size from the morning session to the noon session; and, pupil diameters remained large at the evening session under the 4-mg dose. There were no significant differences between the noon and evening sessions.

As listed in the bottom of Table 34, contrasts for the dose simple effects showed, during both noon and evening sessions, pupil size for both eyes was larger under 4 mg of atropine than under either 2 mg or placebo. Furthermore, pupil diameter was larger during the 2-mg condition than during the placebo condition.

The analysis of variance also revealed dose effects for both pupils ($F(2,22)=28.33$, $p<0.0001$ for the right eye and $F(2,22)=29.01$, $p<0.0001$ for the left eye) and session effects for both pupils ($F(2,22)=109.07$, $p<0.0001$ for the right pupil and $F(2,22)=140.08$, $p<0.0001$ for the left pupil). Contrasts for the session effect revealed pupil diameters for both eyes increased in the noon session when compared to the morning session

Table 33.

Cell means for selected vision battery tests

Variable	Placebo			Dose 2 mg			4 mg		
	Session								
	am	Noon	pm	am	Noon	pm	am	Noon	pm
Right pupil diameter (mm)	3.75	4.00	3.92	3.67	5.08	4.88	3.79	5.67	5.54
Left pupil diameter (mm)	3.75	4.00	3.92	3.67	5.08	4.96	3.79	5.67	5.54
Stereopsis (sec of arc)	37.50	31.30	32.50	43.80	93.80	100.00	43.80	295.00	298.60
Right accommodation (cm)	8.13	7.75	7.94	8.33	6.21	6.49	7.94	3.75	3.82
Left accommodation (cm)	8.13	8.00	7.94	8.20	6.41	6.41	8.00	4.00	3.89
Near lateral phoria*	0.20	0.80	1.10	0.20	4.10	3.00	0.20	8.00	7.20
Near vertical phoria**	0.67	0.58	0.83	0.75	0.92	0.75	0.75	2.00	1.17

* prism diopters of esophoria

** prism diopters of left hyperphoria

Pupil diameters

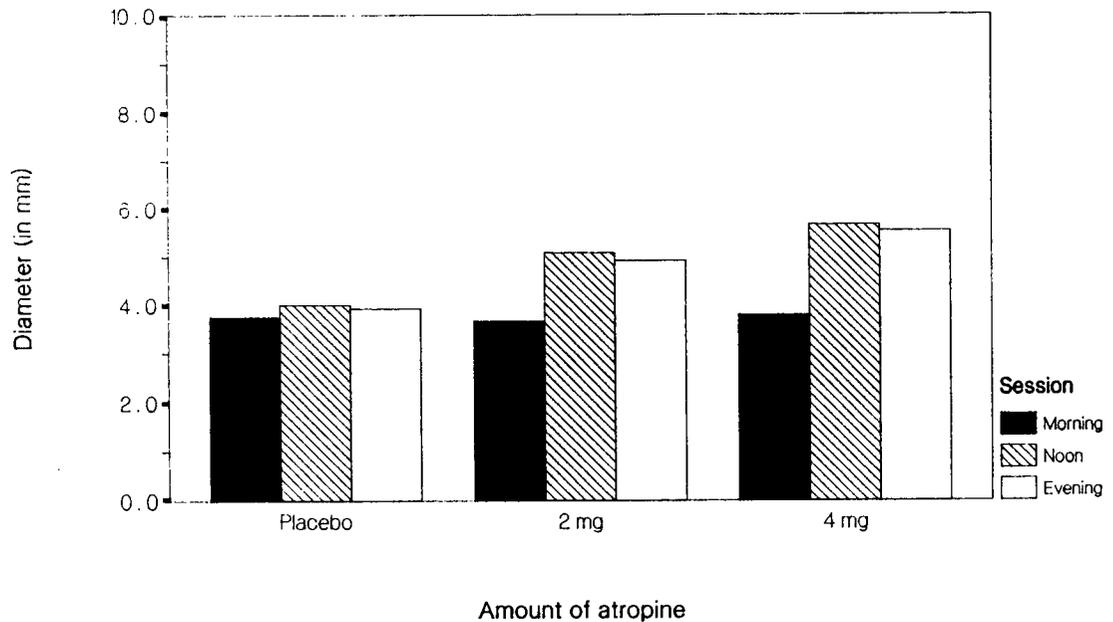


Figure 18. Effects of atropine on pupil diameters.

($F(1,11)=214.22$, $p<0.0001$ for the right pupil and $F(1,11)=214.22$, $p<0.0001$ for the left pupil) and remained large during the evening session ($F(1,11)=116.53$, $p<0.0001$ for the right pupil and $F(1,11)=175.79$, $p<0.0001$ for the left pupil). There were no significant differences between pupil diameters measured during the evening session when compared with the noon session.

Contrasts for the dose effect revealed increases in pupil diameter in both the 2-mg condition and the 4-mg condition relative to the placebo condition, and in the 4-mg condition relative to the 2-mg condition (Table 35).

Stereopsis

Stereopsis was measured using the TNO test for stereoscopic vision. The test consisted of seven plates containing random-dot stereograms presented in two-color anaglyphs (half-images which have been superimposed with controlled disparity and printed in complementary colors). When viewed by a binocular subject through red and green filters, images can be seen in depth. The first four plates allowed the experimenter to screen subjects for the presence of stereoscopic vision. The stereograms in these plates were presented at an angular disparity of 1980 sec (") of

Table 34.

Contrasts for dose by session interaction for pupil diameter.

Contrast		Left pupil		Right pupil	
		F	p	F	p
Session at 2 mg	a.m.-noon	77.54	<0.0001	77.54	<0.0001
	a.m.-p.m.	68.20	<0.0001	40.75	0.0001
	noon-p.m.		NS		NS
Session at 4 mg	a.m.-noon	70.71	<0.0001	70.71	<0.0001
	a.m.-p.m.	107.80	<0.0001	107.80	<0.0001
	noon-p.m.		NS		NS
Dose at noon	0 mg-2 mg	20.89	0.0008	20.89	0.0008
	0 mg-4 mg	42.31	<0.0001	42.31	<0.0001
	2 mg-4 mg	5.34	0.0413	5.34	0.0413
Dose in p.m.	0 mg-2 mg	22.99	0.0006	16.77	0.0018
	0 mg-4 mg	49.35	<0.0001	49.35	<0.0001
	2 mg-4 mg	14.08	0.0032	10.17	0.0086

Table 35.

Contrasts for dose effect for pupil diameter.

Contrast		Left pupil		Right pupil	
		F	p	F	p
Dose	0 mg-2 mg	20.59	0.0008	18.26	0.0013
	0 mg-4 mg	47.83	<0.0001	47.83	<0.0001
	2 mg-4 mg	11.16	0.0066	12.44	0.0047

arc. The three quantitative plates consisted of a set of six pairs of the random-dot stereograms containing targets which could be seen in depth. The subject had to identify the orientation of the target in each stereogram. When viewed at 40 cm, these stereograms gave a range of angular disparities from 480" to 15". There were two stereograms for each disparity. Thus, for a subject to score at a certain disparity, he had to correctly respond to both stereograms. The lowest angular disparity which the subject correctly resolved was considered his score for that session.

Because the angular disparities decreased exponentially, the scores were first transformed to natural logs. These transformed scores were then submitted to a 3 X 3 analysis of variance with repeated measures on each of the two factors, dose and session. One subject was dropped from the analysis because he failed to pass the initial screening plates during his 4-mg evening session.

Results of the analysis (on the remaining 11 subjects) revealed a dose by session interaction for the stereopsis score ($F(2.07, 20.75)=5.50$, $p=0.0114$) because of session effects at the 2-mg dose ($F(2, 20)=4.79$, $p=0.0200$) and the 4-mg dose ($F(1.32, 13.25)=5.81$, $p=0.0242$) as can be seen in Figure 19. There were also dose effects at both the noon session ($F(2, 20)=6.82$, $p=0.0055$) and the evening session ($F(1.30, 13.03)=7.06$, $p=0.0147$). Contrasts are shown in Table 36.

Contrasts for the session effect at the 2-mg dose revealed a decrease in subjects' ability to resolve disparity in both the noon and evening sessions compared to the morning session; however, there was no difference between the noon and evening sessions. Contrasts for the session effect at the 4-mg dose likewise revealed a reduction in depth perception in both the noon and evening sessions compared to the morning session as indicated by a drop in resolution of angular disparity and a continued reduction in stereopsis due to the drug. The difference between the noon session and evening sessions under 4 mg was not significant.

Contrasts for the dose effect at the noon session indicated subjects' ability to perceive depth was reduced under 4 mg of atropine and under 2 mg of atropine when each was compared to the placebo, but not when compared to each other. Contrasts for the dose effect at the evening session revealed the same pattern.

The analysis of variance also revealed a session main effect ($F(1.33, 13.35)=4.73$, $p=0.0395$) and a dose main effect ($F(2, 20)=6.39$, $p=0.0072$). The session effect was due to a reduction in the ability to perceive depth in both the noon and evening sessions as compared to the morning session (Table 37).

Stereopsis

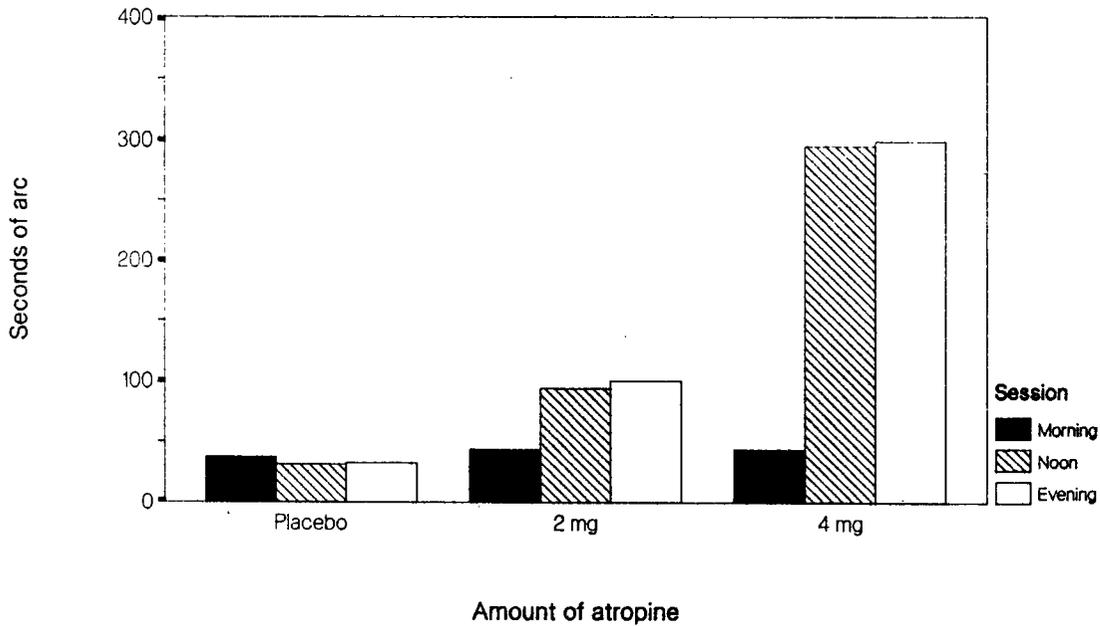


Figure 19. Effects of atropine on stereopsis.

Table 36.

Contrasts for dose X session interaction for stereopsis.

		Contrast	F	p
Session at 2 mg		a.m.-noon	5.21	0.0455
		a.m.-p.m.	9.41	0.0119
		noon-p.m.		NS
Session at 4 mg		a.m.-noon	6.51	0.0288
		a.m.-p.m.	6.35	0.0304
		noon-p.m.		NS
Dose at noon		0 mg-2 mg	5.38	0.0429
		0 mg-4 mg	12.10	0.0059
		2 mg-4 mg		NS
Dose in p.m.		0 mg-2 mg	7.74	0.0194
		0 mg-4 mg	17.71	0.0018
		2 mg-4 mg		NS

Table 37.

Contrasts for session effect for stereopsis.

	Contrast	F	p
Session	a.m.-noon	5.25	0.0450
	a.m.-p.m.	5.25	0.0449
	noon-p.m.		NS

The dose effect was because performance dropped, relative to placebo, in both the 2-mg and 4-mg conditions (Table 38).

Table 38.

Contrasts for dose effect for stereopsis.

	Contrast	F	p
Dose	0 mg-2 mg	5.64	0.0389
	0 mg-4 mg	15.35	0.0029
	2 mg-4 mg		NS

Accommodation

Accommodative ability was measured using a Prince rule. The zero point on the rule was placed approximately 1.5 cm from the cornea. The accommodative target was placed near enough to the eye that the subject could not focus it correctly and then slowly moved away from the eye until the subject could focus it correctly. The distance from the eye was recorded in centimeters; however, accommodation easily can be calculated in diopters by means of the formula:

$$\text{diopters} = 100/\text{cm.}$$

The values for the point of accommodation in centimeters for each subject at each session were submitted to a 3 X 3 analysis of variance with repeated measures on each of the two factors, dose and session. Results of this analysis are displayed (both eyes combined) in Figure 20. They revealed a dose by session

Table 40.

Contrasts for session effect for accommodation.

	Contrast	Left eye		Right eye	
		F	p	F	p
Session	a.m.-noon	15.26	0.0024	22.41	0.0006
	a.m.-p.m.	13.11	0.0040	16.40	0.0019
	noon-p.m.		NS		NS

Table 41.

Contrasts for dose effect for accommodation.

	Contrast	Left eye		Right eye	
		F	p	F	p
Dose	0 mg-2 mg	17.65	0.0015	15.19	0.0025
	0 mg-4 mg	11.92	0.0054	16.05	0.0021
	2 mg-4 mg	8.10	0.0159	11.74	0.0057

Phorias⁹

Vertical and lateral phorias (both near and far) were assessed using the Armed Forces vision testing apparatus. The scale for near and far vertical phorias ranged from one to nine

⁹A phoria is any tendency toward deviation of the eyes from the normal when fusional stimuli are absent or fusion is otherwise prevented....(Dorland, 1981). Both lateral and vertical phorias exist. A lateral deviation towards the nasal midline is termed an "esophoria," whereas one away from the midline is termed an "exophoria." A vertical phoria is named for the eye which is high relative to the other (e.g., a phoria is called "right hyperphoria" regardless of whether the right eye deviates upward or the left eye deviates downward. The Armed Forces vision tester uses a strategy known as "dichoptic viewing," in which the visual scene presented to one eye is so different from the scene presented to the other eye that fusion cannot take place.

Table 37.

Contrasts for session effect for stereopsis.

	Contrast	F	p
Session	a.m.-noon	5.25	0.0450
	a.m.-p.m.	5.25	0.0449
	noon-p.m.		NS

The dose effect was because performance dropped, relative to placebo, in both the 2-mg and 4-mg conditions (Table 38).

Table 38.

Contrasts for dose effect for stereopsis.

	Contrast	F	p
Dose	0 mg-2 mg	5.64	0.0389
	0 mg-4 mg	15.35	0.0029
	2 mg-4 mg		NS

Accommodation

Accommodative ability was measured using a Prince rule. The zero point on the rule was placed approximately 1.5 cm from the cornea. The accommodative target was placed near enough to the eye that the subject could not focus it correctly and then slowly moved away from the eye until the subject could focus it correctly. The distance from the eye was recorded in centimeters; however, accommodation easily can be calculated in diopters by means of the formula:

$$\text{diopters} = 100/\text{cm.}$$

The values for the point of accommodation in centimeters for each subject at each session were submitted to a 3 X 3 analysis of variance with repeated measures on each of the two factors, dose and session. Results of this analysis are displayed (both eyes combined) in Figure 20. They revealed a dose by session

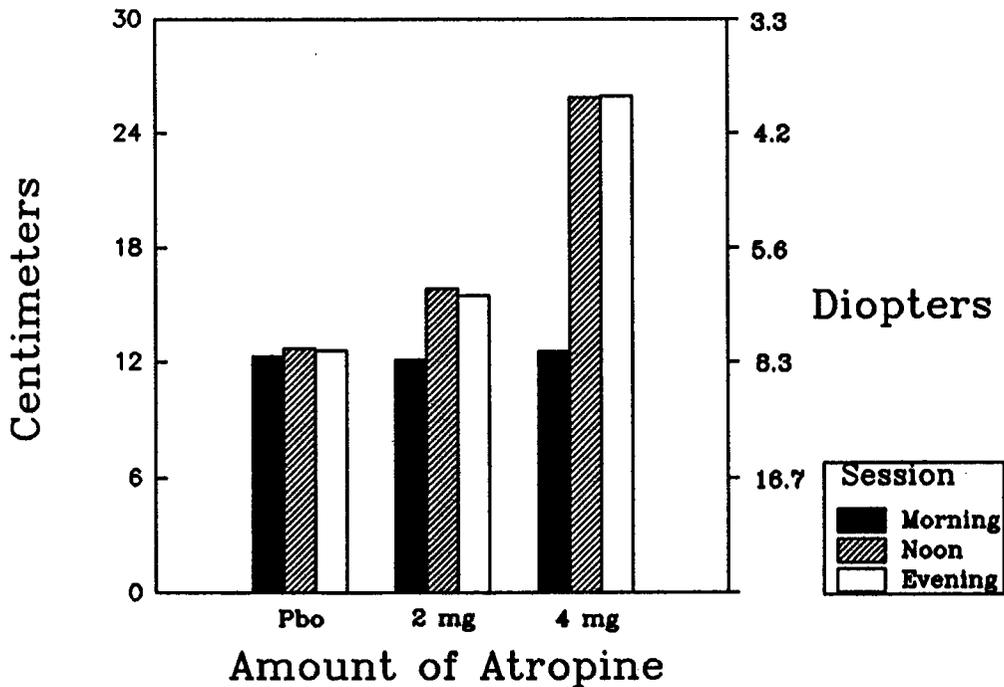


Figure 20. Effects of atropine on accommodation.

interaction for the right eye ($F(1.36,15.00)=11.47, p=0.0022$) and for the left eye ($F(1.55,17.03)=7.98, p=0.0058$), which simple effects revealed were partially due to session effects under the 2-mg dose for each eye (right eye: $F(2,22)=27.73, p<0.0001$ and left eye: $F(2,22)=14.33, p=0.0001$). There also were session effects at the 4-mg dose for both the right eye ($F(1.26,13.86)=13.79, p=0.0015$) and the left eye ($F(2,22)=9.66, p=0.0010$). Furthermore, the analysis revealed a difference attributable to dose at the noon session for each eye ($F(1.05,11.51)=13.31, p=0.0033$ for the right eye and $F(1.06,11.64)=9.60, p=0.0088$ for the left eye) and at the evening session for each eye (right eye: $F(1.06,11.64)=13.29, p=0.0032$ and left eye: $F(1.04,11.49)=9.41, p=0.0097$).

Contrasts for each of the simple effects are shown in Table 39. The session effects at both the 2-mg and 4-mg doses indicated the accommodative power of each eye dropped at noon and in the evening with respect to the morning. The difference between the noon and evening sessions was not significant for either eye. For both the dose at noon and the dose at evening effects, contrasts indicated a significant reduction in accommodative ability with increasing doses of atropine for each eye.

Table 39.

Contrasts for dose X session interaction for accommodation.

	Contrast	Left eye		Right eye	
		F	p	F	p
Session at 2 mg	a.m.-noon	15.66	0.0022	38.66	0.0001
	a.m.-p.m.	18.81	0.0012	24.56	0.0004
	noon-p.m.	NS		NS	
Session at 4 mg	a.m.-noon	11.44	0.0061	15.94	0.0021
	a.m.-p.m.	10.56	0.0077	14.04	0.0032
	noon-p.m.	NS		NS	
Dose at noon	0 mg-2 mg	17.36	0.0016	25.89	0.0004
	0 mg-4 mg	11.51	0.0060	15.50	0.0023
	2 mg-4 mg	7.20	0.0213	10.35	0.0082
Dose in p.m.	0 mg-2 mg	18.65	0.0012	16.95	0.0017
	0 mg-4 mg	11.00	0.0069	15.42	0.0024
	2 mg-4 mg	7.32	0.0205	10.77	0.0073

The analysis also revealed a session effect for each eye (right eye: $F(1.28, 14.09) = 17.56$, $p = 0.0005$ and left eye: $F(1.35, 14.88) = 12.50$, $p = 0.0016$). Furthermore, there was a dose effect for both the right eye ($F(1.06, 11.71) = 14.09$, $p = 0.0026$) and the left eye ($F(1.05, 11.56) = 10.28$, $p = 0.0074$). The session effect was because of better accommodation in the morning compared to either the noon or the evening, but the later sessions did not differ from one another (Table 40).

Contrasts for the dose main effect indicated accommodation was reduced in the 2-mg and 4-mg conditions as compared to the placebo condition. Also, accommodation under 2 mg was better than under 4 mg (Table 41).

Table 40.

Contrasts for session effect for accommodation.

	Contrast	Left eye		Right eye	
		F	p	F	p
Session	a.m.-noon	15.26	0.0024	22.41	0.0006
	a.m.-p.m.	13.11	0.0040	16.40	0.0019
	noon-p.m.	NS		NS	

Table 41.

Contrasts for dose effect for accommodation.

	Contrast	Left eye		Right eye	
		F	p	F	p
Dose	0 mg-2 mg	17.65	0.0015	15.19	0.0025
	0 mg-4 mg	11.92	0.0054	16.05	0.0021
	2 mg-4 mg	8.10	0.0159	11.74	0.0057

Phorias⁹

Vertical and lateral phorias (both near and far) were assessed using the Armed Forces vision testing apparatus. The scale for near and far vertical phorias ranged from one to nine

⁹A phoria is any tendency toward deviation of the eyes from the normal when fusional stimuli are absent or fusion is otherwise prevented....(Dorland, 1981). Both lateral and vertical phorias exist. A lateral deviation towards the nasal midline is termed an "esophoria," whereas one away from the midline is termed an "exophoria." A vertical phoria is named for the eye which is high relative to the other (e.g., a phoria is called "right hyperphoria" regardless of whether the right eye deviates upward or the left eye deviates downward. The Armed Forces vision tester uses a strategy known as "dichoptic viewing," in which the visual scene presented to one eye is so different from the scene presented to the other eye that fusion cannot take place.

with a value of five representing orthophoria. Every unit increase above five on the scale represents a 0.5 prism diopter increase in right hyperphoria. Every unit decrease below five on the scale represents a 0.5 prism diopter increase in left hyperphoria. The scale for near lateral phoria ranged asymmetrically from 0 to 34 with a value of 13 representing orthophoria. The scale for far lateral phoria ranged from 0 to 22 with 11 representing orthophoria. Every unit decrease below the orthophoric value represents a 1.0 prism diopter increase in esophoria. Every unit increase above the orthophoric value on the lateral phoria scales represents a 1.0 prism diopter increase in exophoria.

The subjects' reported values from each of the four scales for each session were analyzed in four separate 3 X 3 repeated measures analyses of variance. There were no significant effects revealed by the analyses for far lateral phoria or far vertical phoria. However, the results of the analysis for near lateral phoria revealed a dose by session interaction ($F(4,44)=10.18$, $p<0.0001$), a dose effect ($F(2,22)=17.03$, $p<0.0001$), and a session effect ($F(1.25,13.71)=30.83$, $p<0.0001$).

The dose by session interaction (shown graphically in Figure 21) was due to session effects at the 2-mg dose ($F(2,22)=8.36$, $p=0.0020$) and at the 4-mg dose ($F(1.34,14.72)= 32.11$, $p<0.0001$).

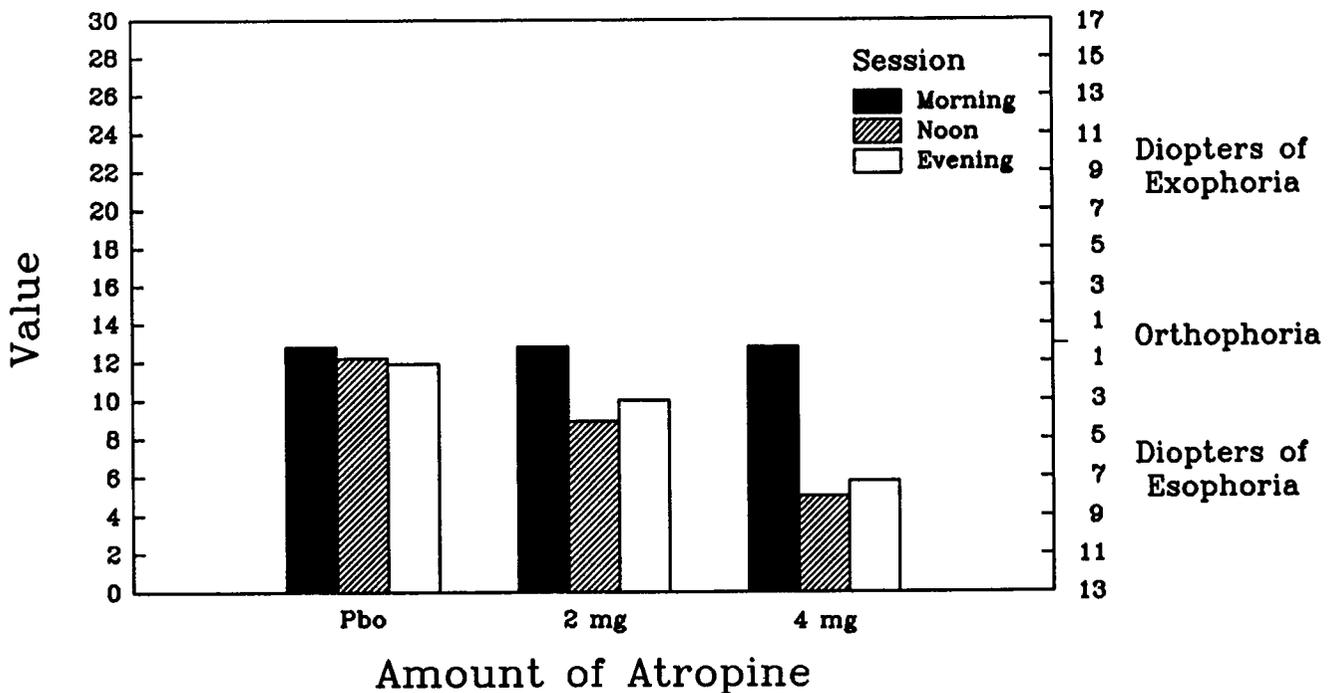


Figure 21. Effects of atropine on near lateral phoria.

The session effect contrasts revealed differences between the morning session and both the noon and evening sessions for

Table 43.

Contrasts for dose X session interaction for near vertical phoria.

=====			
	Contrast	F	p

Session at 4 mg	a.m.-noon	7.89	0.0172
	a.m.-p.m.		NS
	noon-p.m.		NS
=====			
Dose at noon	0 mg-2 mg	5.50	0.0388
	0 mg-4 mg	9.84	0.0095
	2 mg-4 mg		NS
=====			

near lateral phoria (Table 44). Thus, esophoria increased at both of the later sessions. Examination of the session effect for near vertical phoria confirmed the results of the dose by session interaction discussed earlier (Table 44). Subjects were more likely to exhibit left hyperphoria during the noon session than during the morning session, whereas there were no differences in this measure elsewhere.

Table 44.

Contrasts for session effect for near lateral phoria.

=====					
	Contrast	Lateral		Vertical	
		F	p	F	p

Session	a.m.-noon	33.64	0.0001	5.50	0.0388
	a.m.-p.m.	32.84	0.0001		NS
	noon-p.m.		NS		NS
=====					

Contrasts for the dose effect indicated increases in esophoria for the 2-mg and 4-mg conditions relative to the

placebo condition for near lateral phoria (Table 45). Furthermore, the increase in esophoria in the 4-mg condition was greater than that in the 2-mg condition. Finally, contrasts for the dose effect for near vertical phoria indicated subjects were more likely to be left hyperphoric after administration of 4 mg of atropine than after administration of either 2 mg or the placebo (Table 45).

Table 45.

Contrasts for dose effect for near lateral phoria.

=====					
Contrast		Lateral		Vertical	
		F	p	F	p

Dose	0 mg-2 mg	5.37	0.0407	NS	
	0 mg-4 mg	32.65	0.0001	6.56	0.0265
	2 mg-4 mg	12.10	0.0052	5.21	0.0433
=====					

Contrast sensitivity

Static contrast sensitivity was measured using the Vistech contrast test system. Scores were obtained for each given spatial frequency using the appropriate charts at 10 feet for distant vision and 16 inches for near vision. The charts present five rows of sinusoidal grating patterns arranged in order of increasing spatial frequency. The spatial frequencies tested were 1.5, 3, 6, 12, and 18 cycles per degree (cpd). Each row contained eight grating patterns of decreasing contrast and different orientation (left, up, or right), and a ninth pattern which had a contrast of zero. The subjects' scores for the task were the highest contrast sensitivities obtained for each spatial frequency at each session. Scores for the near and far contrast sensitivity tests were transformed to the log contrast for each spatial frequency. A constant of 1.00 was added to each subject's near contrast sensitivity (NCS) score before log transformations were performed because one subject obtained a value of 0 for his NCS score at 18 cpd. These transformed scores were analyzed using two separate 3 X 3 X 5 analyses of variance with repeated measures on dose, session, and cycles per degree (cpd).

Near contrast sensitivity

Results of the analysis of near contrast sensitivity revealed a dose by session interaction ($F(2.10,23.06)=5.97$, $p=0.0075$) and a dose by cpd interaction ($F(8,88)=3.49$, $p=0.0015$). There were also main effects for dose ($F(1.31,14.37)=6.13$, $p=0.0200$), session ($F(1.28,14.10)=9.62$, $p=0.0052$), and cpd ($F(1.99,21.86)=117.42$, $p<0.0001$).

The dose by session interaction was due to dose effects during the morning session ($F(2,22)=6.99$, $p=0.0045$), during the noon session ($F(1.32,14.56)=6.72$, $p=0.0151$), and during the evening session ($F(1.24,13.61)=5.33$, $p=0.0314$). Furthermore, there were session effects at the 2-mg dose condition ($F(2,22)=9.54$, $p=0.0010$) and the 4-mg dose condition ($F(2,22)=8.79$, $p=0.0016$). The dose by cpd interaction was because of dose effects at 6 cpd ($F(2,22)=6.25$, $p=0.0071$), at 12 cpd ($F(1.27,13.94)=8.18$, $p=0.0092$), and at 18 cpd ($F(1.32,14.53)=5.21$, $p=0.0302$). In addition, there were cpd effects for the placebo condition ($F(2.25,24.70)=87.27$, $p<0.0001$), the 2-mg condition ($F(2.25,24.73)=69.71$, $p<0.0001$), and the 4-mg condition ($F(1.52,16.73)=46.13$, $p<0.0001$).

Contrasts for the dose by session interaction (top of Table 46) indicated the mean contrast sensitivity was greater for the 2-mg morning session than it was for the placebo morning session; but, the mean for the 4-mg morning session was not different from the others. Reasons for such an effect remain unclear at this point.

During the noon session, subjects displayed greater contrast sensitivity in both the placebo and 2-mg conditions as compared to the 4-mg condition. There were no differences between the 2-mg and placebo conditions. During the evening session, only the decrease from placebo to 4 mg was significant.

Looking at this interaction from the other direction (bottom of Table 46), there were no differences between sessions for the placebo condition, but contrast sensitivity under 2 mg was greater during the morning session than during either the noon or the evening session. There was, however, no difference between these last two sessions. Results of contrasts for the 4-mg condition were essentially the same.

Contrasts for the dose by cpd interaction indicated differences between dose conditions at the higher spatial frequencies (Table 47 and Figure 23). At 6 cpd, for example, 4 mg of atropine produced degradation of contrast sensitivity relative to both placebo and 2 mg of atropine, but there was no difference between the placebo condition and the 2-mg condition. The same results were found at 12 cpd and 18 cpd. Examined

Table 46.

Contrasts for dose X session interaction
for near contrast sensitivity.

	Contrast	F	p
Dose in a.m.	0 mg-2 mg	17.44	0.0015
	0 mg-4 mg		NS
	2 mg-4 mg		NS
Dose at noon	0 mg-2 mg		NS
	0 mg-4 mg	7.67	0.0183
	2 mg-4 mg	6.96	0.0231
Dose in p.m.	0 mg-2 mg		NS
	0 mg-4 mg	6.54	0.0266
	2 mg-4 mg		NS
Session at 2 mg	a.m.-noon	17.34	0.0016
	a.m.-p.m.	10.96	0.0070
	noon-p.m.		NS
Session at 4 mg	a.m.-noon	12.48	0.0047
	a.m.-p.m.	8.52	0.0140
	noon-p.m.		NS

another way, in the placebo condition, there were differences between all spatial frequencies except for 3 cpd and 6 cpd (Table 48). In the 2-mg condition, there were differences between all spatial frequencies, and in the 4-mg condition, there were differences between all spatial frequencies except between 1.5 cpd and 12 cpd and between 3 cpd and 6 cpd.

The dose effect was due to a worsening of contrast sensitivity under the 4-mg dose as compared to the 2-mg and placebo doses (Table 49). There was, however, no difference between the 2-mg condition and the placebo condition. The session effect was because of differences between the morning session and both the noon and evening sessions (Table 50). There was no difference between the noon and the evening session. The cpd effect on near contrast sensitivity was due to differences between all spatial frequencies except 3 and 6 cpd (Table 51).

Table 47.

Dose contrasts for dose X CPD interaction
for near contrast sensitivity.

		Contrast	F	p
Dose at 6 cpd		0 mg-2 mg		NS
		0 mg-4 mg	6.82	0.0242
		2 mg-4 mg	8.49	0.0141
Dose at 12 cpd		0 mg-2 mg		NS
		0 mg-4 mg	7.94	0.0167
		2 mg-4 mg	10.37	0.0082
Dose at 18 cpd		0 mg-2 mg		NS
		0 mg-4 mg	5.48	0.0391
		2 mg-4 mg	6.35	0.0285

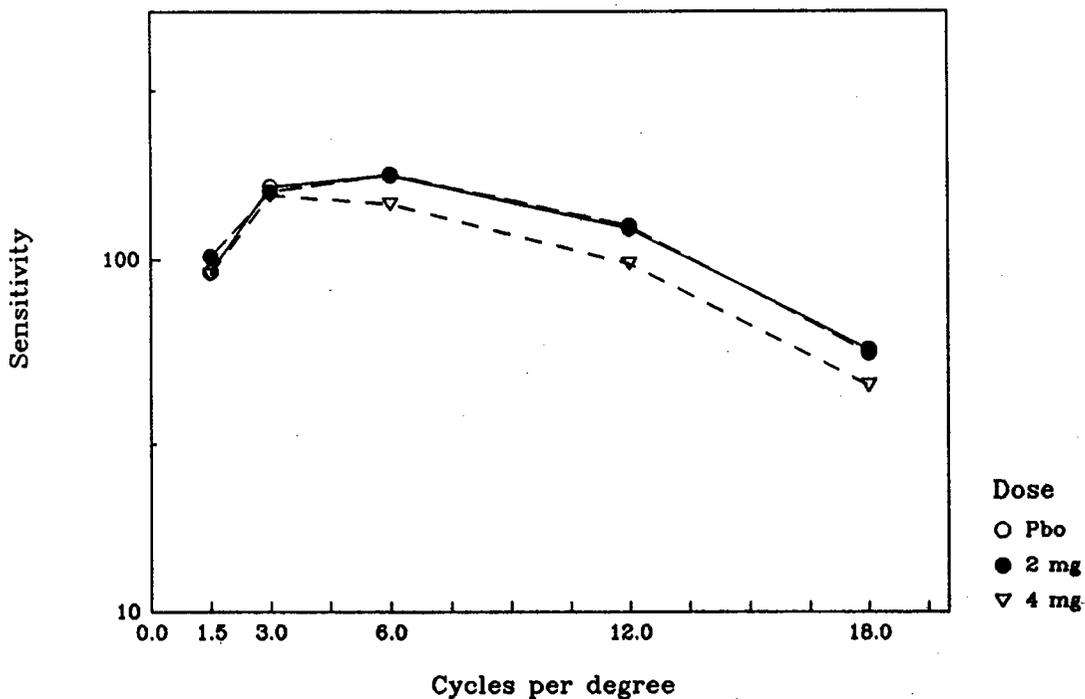


Figure 23. Effects of atropine on near contrast sensitivity.

Table 48.

CPD contrasts for dose X CPD interaction
for near contrast sensitivity.

		Contrast	F	p
CPD at placebo		1.5-3	39.42	0.0001
		1.5-6	93.69	<0.0001
		1.5-12	20.90	0.0008
		1.5-18	26.69	0.0003
		3 - 6		NS
		3 -12	53.92	<0.0001
		3 -18	224.59	<0.0001
		6 -12	176.24	<0.0001
		6 -18	199.77	<0.0001
		12 -18	106.99	<0.0001
CPD at 2 mg		1.5- 3	46.39	<0.0001
		1.5- 6	50.72	<0.0001
		1.5-12	11.03	0.0068
		1.5-18	26.83	0.0003
		3 - 6	6.94	0.0232
		3 -12	8.07	0.0161
		3 -18	110.36	<0.0001
		6 -12	23.03	0.0006
		6 -18	195.88	<0.0001
		12 -18	255.31	<0.0001
CPD at 4 mg		1.5- 3	61.47	<0.0001
		1.5- 6	28.12	0.0003
		1.5-12		NS
		1.5-18	32.49	0.0001
		3 - 6		NS
		3 -12	14.00	0.0033
		3 -18	59.71	<0.0001
		6 -12	43.69	<0.0001
		6 -18	144.91	<0.0001
		12 -18	133.85	<0.0001

Table 49.

Contrasts for dose effect for near contrast sensitivity.

	Contrast	F	p
	0 mg-2 mg	NS	
Dose	0 mg-4 mg	5.85	0.0341
	2 mg-4 mg	8.38	0.0146

Table 50.

Contrasts for session effect for near contrast sensitivity.

	Contrast	F	p
	a.m.-noon	12.43	0.0047
Session	a.m.-p.m.	9.45	0.0106
	noon-p.m.	NS	

Table 51.

Contrasts for CPD effect for near contrast sensitivity.

	Contrast	F	p
	1.5- 3	91.31	<0.0001
	1.5- 6	99.20	<0.0001
	1.5-12	8.88	0.0125
	1.5-18	41.20	<0.0001
CPD	3 - 6	NS	
	3 -12	29.70	0.0002
	3 -18	190.39	<0.0001
	6 -12	104.55	<0.0001
	6 -18	410.43	<0.0001
	12 -18	285.68	<0.0001

Far contrast sensitivity

Results of the analysis of variance for the far contrast sensitivity test revealed a dose by session interaction ($F(4,44)=6.25, p=0.0004$), but none of the other interactions was significant. The only significant main effect was found on the cpd factor ($F(2.26,24.87)=202.12, p<0.0001$). Analysis of simple effects for the dose by session interaction indicated a dose effect at the noon session ($F(2,22)=4.48, p=0.0234$) and at the evening session ($F(2,22)=6.87, p=0.0048$). Furthermore, there was a session effect at 4 mg ($F(2,22)=12.99, p=0.0002$), but there were no session effects at 2 mg or placebo.

Contrasts for these effects showed a decrease in contrast sensitivity at the noon session under 4 mg of atropine when compared to placebo, while none of the other dose conditions differed here. For the evening session, contrast sensitivity was degraded by 4 mg of atropine when compared to both placebo and 2 mg of atropine, but the difference between the 2-mg condition and the placebo condition was not significant (upper portion of Table 52). The differences in sessions under the 4-mg dose were attributed to reduced contrast sensitivity at both the noon and evening sessions in comparison to the morning session (lower portion of Table 52). The significant main effect on the cpd factor was because contrast sensitivity at each spatial frequency differed from contrast sensitivity at all the others (Table 53).

Table 52.

Contrasts for dose X session interaction
for far contrast sensitivity.

=====			
	Contrast	F	p

Dose at noon	0 mg-2 mg		NS
	0 mg-4 mg	11.77	0.0056
	2 mg-4 mg		NS

Dose in p.m.	0 mg-2 mg		NS
	0 mg-4 mg	9.98	0.0091
	2 mg-4 mg	5.45	0.0395
=====			
Session at 4 mg	a.m.-noon	19.62	0.0010
	a.m.-p.m.	21.08	0.0008
	noon-p.m.		NS
=====			

Table 53.

Contrasts for CPD effect for far contrast sensitivity.

=====			
	Contrast	F	p

	1.5- 3	112.39	<0.0001
	1.5- 6	145.12	<0.0001
	1.5-12	23.60	0.0005
	1.5-18	64.93	<0.0001
CPD	3 - 6	18.36	0.0013
	3 -12	24.79	0.0004
	3 -18	488.19	<0.0001
	6 -12	117.84	<0.0001
	6 -18	1056.45	<0.0001
	12 -18	627.86	<0.0001
=====			

Near point of convergence

This measure was obtained using the Prince rule and an accommodative target. The target was brought toward the subject until the observer noted the subject could no longer maintain convergence. The data were unsuitable for parametric analysis; however, they were interesting to consider in relation to the number of instances subjects failed to meet aeromedical standards for vision. U.S. Army aeromedical standards call for pilots to have a near point of convergence (NPC) of less than 7 cm. Two of the 12 subjects had NPCs greater than 7 cm even during their placebo sessions. Neither the 2-mg dose nor the 4-mg dose produced increases in NPC for any of the subjects.

Fusion

Gross visual fusion ability was assessed using the Worth four-dot test, a standard screening test. While 2 mg of atropine failed to disrupt subjects' ability to fuse, 4 mg produced a loss of fusion and complaints of double vision in 3 of the 12 subjects.

Visual acuity

Far visual acuity was assessed using the (Sanyo) True visual acuity vision analyzer computer, while near visual acuity was assessed using the near vision test chart. Data from these tests

were also unsuitable for parametric analysis; therefore, they will be presented in terms of frequencies. U.S. Army aeromedical standards call for pilots to have at least 20/20 visual acuity, both near and far. Neither the 2-mg dose nor the 4-mg dose of atropine affected far visual acuity. The 2-mg dose had no effect on near visual acuity either. However, 5 of the 12 subjects had less than 20/20 near visual acuity under the influence of 4 mg of atropine.

Electroencephalographic activity

Electroencephalographic data were collected from a full International 10-20 electrode montage so subsequent brain mapping could be performed with the Cadwell Spectrum 32 to assess the overall extent of cortical activation under atropine. Data were collected during eyes-open followed by eyes-closed (60 seconds each), after which spectral analyses were performed on relatively artifact free, 2.5 second epochs. For purposes of statistical analyses, only the midline electrodes were examined. The percentage of delta, theta, alpha, and beta, the ratio of fast-to-slow activity, and the mean frequency from F_z , C_z , P_z , and O_z were examined because the first four values provide a fairly precise insight into the overall frequency of EEG activity from slow waves (sleep or relaxation) to fast waves (thinking or concentration). The last two values provide a less precise overview of the information contained in the individual frequency bands. These data were analyzed with a series of three-way analyses of covariance with dose (placebo, 2 mg, 4 mg), session (noon, evening), and eyes (open, closed) as factors. The covariates were the data collected from the morning (predose) session of the same dosage administration day. Missing data due to equipment failures and occasional excessive artifact were estimated by BMDPAM using the mean for those variables. All percentage data were transformed using the arcsin transformation discussed earlier.

Before presenting the results of each independent analysis, a point about the analysis of covariance procedure should be noted. For some reason, use of the morning session data as covariates resulted in failure to detect significant differences from eyes-open activity to eyes-closed activity, particularly in the alpha band. In most cases, where a large difference was expected (between open and closed), the effect of the covariate was tremendous, but the "eyes" effect was insignificant. To be on the safe side, many of the analyses were rerun without the use of covariance procedures. When this was done, the differences from eyes-open to eyes-closed did attain significance where such differences were expected. Also, most of the other effects, found earlier with covariance procedures, did not appear to

change. Thus, we will simply report this statistical exercise so the reader won't be left wondering why we didn't discuss the expected differences in EEG activity from eyes-open to eyes-closed; however, we will continue to rely on the analysis of covariance results to explain the other effects. In the future, it would be advisable to analyze EEG data with more straightforward ANOVA procedures.

Frontal EEG activity

Analysis of the percentage of activity contributed by each of the major EEG bands at F_z revealed a number of effects. Delta activity was affected by atropine ($F(2,21)=6.35, p=0.007$) in that there was more slow-wave activity under both 4 mg and 2 mg than there was under placebo (Table 54). Also, there was a decline in delta activity in eyes-closed compared to eyes-open ($F(1,10)=4.95, p=0.0503$). Some of this may have been partially due to reduced chances of eye movements even though each epoch was scanned visually for artifact elimination. Theta at F_z was unaffected by dose, but showed a reduction in the evening session with respect to the noon session ($F(1,11)=4.80, p=0.0509$).

Table 54.

Contrasts for dose effect for EEG: F_z , delta.

	Contrast	F	p
	0 mg-2 mg	6.89	0.0254
Dose	0 mg-4 mg	19.03	0.0014
	2 mg-4 mg	NS	

The percentage of alpha activity revealed a three-way interaction between dose, session, and eyes ($F(2,22)=4.02, p=0.0325$) and a two-way interaction between dose and eyes ($F(2,21)=4.35, p=0.0263$). There were also main effects for dose ($F(2,21)=5.32, p=0.0136$) and session ($F(1,11)=7.36, p=0.0202$). Analysis of simple effects indicated the three-way interaction was attributable to a difference among doses during eyes-open at only the evening session ($F(2,21)=9.83, p=0.001$) which was due to differences between placebo and 2 mg, and between 2 mg and 4 mg (Table 55). The two-way interaction between dose and eyes was found to be due to effects at both eyes-closed ($F(2,21)=5.67, p=0.0108$) and eyes-open ($F(2,21)=4.03, p=0.0331$).

Table 55.

Contrasts for dose X session X eyes interaction
for EEG: F_2 , alpha.

	Contrast	F	p
Dose in evening, eyes open	0 mg-2 mg	8.52	0.0153
	0 mg-4 mg	NS	
	2 mg-4 mg	13.13	0.0047

The dose effect at eyes-closed was due to a reduction in alpha under 4 mg compared to placebo, whereas the effect at eyes-open resulted from a decrease in alpha in the 4-mg condition compared to the 2-mg condition (Table 56). The session effect was due to an increase in alpha from the noon to the evening session, and the main effect attributable to dose was a result of lower alpha under the 4-mg dose than under either the 2-mg dose or placebo (Table 57).

Table 56.

Contrasts for dose X eyes interaction for EEG: F_2 , alpha.

	Contrast	F	p
Dose with eyes open	0 mg-2 mg	NS	
	0 mg-4 mg	NS	
	2 mg-4 mg	7.25	0.0226
Dose with eyes closed	0 mg-2 mg	NS	
	0 mg-4 mg	10.39	0.0090
	2 mg-4 mg	NS	

The analyses conducted on the percentage of beta activity at F_2 revealed almost no effects. In fact, the only detectable difference in this fast activity occurred because of opening and closing the eyes where there was more beta during eyes-open than during eyes-closed, as would have been expected.

Table 57.

Contrasts for dose main effect for EEG: F_2 , alpha.

=====			
	Contrast	F	p

	0 mg-2 mg	NS	
Dose	0 mg-4 mg	9.03	0.0132
	2 mg-4 mg	6.14	0.0326
=====			

The ratio of fast to slow activity at F_2 indicated there was a general EEG slowing attributable to dose ($F(2,21)=5.59$, $p=0.0113$) and session ($F(1,11)=7.63$, $p=0.0185$). The session effect resulted from slower EEG activity during the noon session in comparison to the evening session. The dose effect was because of slower activity under the 4-mg dose than under either the 2-mg or placebo doses (Table 58).

Table 58.

Contrasts for dose effect for EEG: F_2 , ratio.

=====			
	Contrast	F	p

	0 mg-2 mg	NS	
Dose	0 mg-4 mg	6.13	0.0328
	2 mg-4 mg	8.68	0.0146
=====			

The analysis of mean frequency at F_2 did not reveal the significant atropine-related slowing of EEG seen with the ratio data above. However, the slowing of activity at the noon session relative to the evening session was supported ($F(1,11)=6.91$, $p=0.0235$).

Central EEG activity

Analysis of the EEG activity detected at C_z revealed at least some effects on every measure with the exception of ratio of fast- to-slow activity. The amount of delta activity was higher during eyes-open than during eyes-closed (F(1,10)=12.51, p=0.0054), an effect which could have been partially due to the increased chance of eye movements (although it's unlikely at an electrode this far removed from the eyes). Also, the percentage of delta was affected by dose (F(2,21)=4.01, p=0.0335) in that 4 mg of atropine was associated with greater amounts of delta than was placebo (Table 59).

Table 59.

Contrasts for dose effect for EEG: C_z, delta.

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	Contrast	F	p
	0 mg-2 mg		NS
Dose	0 mg-4 mg	12.40	0.0055
	2 mg-4 mg		NS

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The percentage of theta activity was impacted only by the time of day at which testing occurred. This could be seen from the session effect (F(1,11)=4.87, p=0.0495) due to the presence of more theta during the noon session than during the evening session.

Alpha activity at C_z was affected in more complex ways than was theta. There was an interaction among dose, session, and eyes (F(2,22)=4.24, p=0.0278), and a tendency toward an interaction between dose and eyes (F(2,21)=3.32, p=0.0559). Simple effects revealed the three-way interaction resulted from a dose effect (F(2,21)=6.24, p=0.0074) at the evening session during eyes-open due to differences between placebo and 2 mg, and between 2 mg and 4 mg where the 2-mg dose was associated with higher alpha than the other two (Table 60). The two-way interaction between dose and eyes was attributable to a dose effect (F(2,21)=6.14, p=0.0079) at eyes-closed, found to be a result of more alpha under placebo than both 2 mg and 4 mg of atropine (Table 61). There was also an overall dose effect (F(2,21)=3.59, p=0.0457) because of a significant reduction in alpha activity under the 4-mg dose in comparison to placebo (Table 62).

Table 60.

Contrasts for dose X session X eyes interaction for EEG: C₂, alpha.

	Contrast	F	p
Dose in	0 mg-2 mg	5.08	0.0478
evening,	0 mg-4 mg		NS
eyes open	2 mg-4 mg	9.36	0.0120

Table 61.

Contrasts for dose X eyes interaction for EEG: C₂, alpha.

	Contrast	F	p
Dose with	0 mg-2 mg	7.88	0.0186
eyes	0 mg-4 mg	17.76	0.0018
closed	2 mg-4 mg		NS

Table 62.

Contrasts for dose effect for EEG: C₂, alpha.

	Contrast	F	p
	0 mg-2 mg		NS
Dose	0 mg-4 mg	8.81	0.0141
	2 mg-4 mg		NS

Beta activity was relatively unaffected by any of the factors under investigation. The one exception to this was an effect ($F(1,10)=10.50$, $p=0.0089$) due to decreased beta with eyes-closed as opposed to eyes-open.

The ratio of fast-to-slow activity at C_z was shifted as a function of the dose ($F(2,21)=3.96, p=0.0347$), and subsequent contrasts revealed this effect to be due to a decrease in the ratio under 4 mg as compared to the ratio under placebo (Table 63). This finding is consistent with what was observed elsewhere.

Table 63.

Contrasts for dose effect for EEG: C_z , ratio.

	Contrast	F	p
	0 mg-2 mg		NS
Dose	0 mg-4 mg	5.11	0.0473
	2 mg-4 mg		NS

Mean frequency of the EEG was not affected by dose, session, or eyes-open/eyes-closed at C_z . Furthermore, there were no interactions among these factors.

Parietal EEG activity

Analyses of the EEG activity from P_z showed effects similar to those seen at the other electrode sites. The percentage of delta activity was significantly affected by dose ($F(2,21)=7.25, p=0.0040$), and eyes ($F(1,10)=8.70, p=0.0145$). The dose effect was because of increased delta under the 4-mg dose in comparison to the placebo dose (Table 64). The eyes effect was due to a downward shift in the amount of delta from eyes-open to eyes-closed.

Whereas theta activity was unaffected at both F_z and C_z , at P_z the percentage of theta was increased in a manner similar to what was seen with delta activity at this lead. The effect ($F(2,21)=5.50, p=0.0120$) was largely attributable to the 4-mg dose which was associated with much more theta than was obtained under either the 2-mg dose or the placebo dose (Table 65).

Alpha activity at P_z was affected only marginally by the combination of dose, session, and eyes ($F(2,22)=3.27, p=0.0578$), but was affected markedly by the combination of dose and eyes ($F(2,21)=4.37, p=0.0259$). Simple effects revealed the three-way interaction was due to a dose effect during the noon session at

Table 64.

Contrasts for dose effect for EEG: P_z, delta.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	38.36	0.0001
	2 mg-4 mg		NS
=====			

Table 65.

Contrasts for dose effect for EEG: P_z, theta.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	9.03	0.0132
	2 mg-4 mg	9.75	0.0108
=====			

eyes-closed ($F(2,21)=5.41$, $p=0.0127$), and a dose effect during the evening session at eyes-open ($F(2,21)=3.77$, $p=0.04$). During the noon session, the effect was attributable to differences between the 4-mg (least alpha) and placebo (most alpha) conditions; but during the evening session, the effect was because of a difference between the 4-mg (least alpha) and 2-mg (most alpha) doses (Table 66).

The two-way interaction between dose and eyes was found to be due to a dose effect at eyes-closed ($F(2,21)=10.04$, $p=0.0009$) which was because of progressive reductions in alpha with increasing doses of atropine (Table 67).

Finally, there were main effects relating to session ($F(1,11)=9.21$, $p=0.0113$) and dose ($F(2,21)=7.95$, $p=0.0027$). The session effect was due to increases in alpha activity in the evening with respect to noon, while the dose effect was because of significant alpha reductions under 4 mg in comparison to both placebo and 2 mg (Table 68).

Table 66.

Contrasts for dose X session X eyes interaction for EEG: P₂, alpha.

	Contrast	F	p
Dose at noon, eyes closed	0 mg-2 mg		NS
	0 mg-4 mg	11.20	0.0074
	2 mg-4 mg		NS
Dose in p.m., eyes open	0 mg-2 mg		NS
	0 mg-4 mg		NS
	2 mg-4 mg	6.53	0.0286

Table 67.

Contrasts for dose X eyes interaction for EEG: P₂, alpha.

	Contrast	F	p
Dose with eyes closed	0 mg-2 mg	6.08	0.0333
	0 mg-4 mg	22.55	0.0008
	2 mg-4 mg	5.08	0.0478

Table 68.

Contrasts for dose effect for EEG: P₂, alpha.

	Contrast	F	p
Dose	0 mg-2 mg		NS
	0 mg-4 mg	18.20	0.0016
	2 mg-4 mg	7.20	0.0230

Parietal beta activity revealed an interaction between dose and eyes ($F(2,21)=3.54$, $p=0.0473$) and a main effect on the eyes factor ($F(1,10)=8.64$, $p=0.0148$). Attempts to locate the precise nature of the interaction between dose and eyes were not successful because the analyses of simple effects for dose at eyes-open and dose at eyes-closed were not significant. Therefore, no contrasts were performed. The effect on the eyes factor was due to a reduction in the percentage of beta activity under eyes-closed in comparison to eyes-open.

The ratio of fast-to-slow activity at P_z revealed a tendency toward an interaction between dose and eyes ($F(2,21)=3.30$, $p=0.0568$), a main effect on the eyes factor ($F(1,10)=6.80$, $p=0.0261$), and a main effect on the dose factor ($F(2,21)=8.70$, $p=0.0018$). The two-way interaction involving dose and eyes was found to be a result of a dose effect at both eyes-open ($F(2,21)=3.36$, $p=0.0546$) and eyes-closed ($F(2,21)=9.41$, $p=0.0012$). Contrasts showed a decrease in the ratio of fast-to-slow activity at eyes-open under 4 mg compared to 2 mg atropine, whereas the difference at eyes-closed was due to a decrease under 4 mg atropine compared to the placebo (Table 69).

Table 69.

Contrasts for dose X eyes interaction for EEG: P_z , ratio.

=====			
	Contrast	F	p

Dose with eyes open	0 mg-2 mg		NS
	0 mg-4 mg		NS
	2 mg-4 mg	5.74	0.0375

Dose with eyes closed	0 mg-2 mg		NS
	0 mg-4 mg	21.56	0.0009
	2 mg-4 mg		NS
=====			

The main effect on dose was due to a significant difference between placebo (greatest ratio of fast-to-slow) and 4 mg atropine (least ratio) as seen in Table 70. The main effect on the eyes factor was due to a curious increase in the ratio of fast-to-slow activity from eyes-open to eyes-closed.

The mean frequency at P_z was affected by the dose conditions ($F(2,21)=4.75$, $p=0.0199$) and whether the subject's eyes were open or closed ($F(1,10)=5.92$, $p=0.0352$). The dose effect was due to a

Table 70.

Contrasts for dose effect for EEG: P_z, ratio.

	Contrast	F	p
	0 mg-2 mg		NS
Dose	0 mg-4 mg	26.08	0.0005
	2 mg-4 mg		NS

significant reduction in mean frequency under the 4-mg dose relative to placebo (Table 71). The eyes effect was due to an upward frequency shift from eyes-open to eyes-closed, which is probably partially due to the variance being twice as large under eyes-closed as under eyes-open.

Table 71.

Contrasts for dose effect for EEG: P_z, mean.

	Contrast	F	p
	0 mg-2 mg		NS
Dose	0 mg-4 mg	5.32	0.0438
	2 mg-4 mg		NS

Occipital EEG activity

The EEG recorded at O_z was somewhat different from what was observed in the other leads although the general trend was similar. The major difference showed delta activity unaffected by any of the factors under investigation.

The percentage of theta was affected by the combination of dose and session ($F(2,22)=13.41, p=0.0002$) which analysis of simple effects pinpointed as due to the presence of a dose effect during the noon session ($F(2,21)=18.86, p<0.0001$) that was not present during the evening session. Subsequent contrasts showed the dose effect at noon was due to increased theta associated with increasing amounts of atropine (Table 72). All comparisons were significant. Also, there was an overall dose effect with

theta ($F(2,21)=7.22$, $p=0.0041$) because of higher amounts of this activity under 4 mg than under both 2 mg and placebo (Table 73).

Alpha activity was affected somewhat differently in that there were no interactions, but there were two main effects. There was a difference in alpha as a function of dose ($F(2,21)=7.76$, $p=0.0030$) and session ($F(1,11)=4.78$, $p=0.0513$). The dose effect was due to less alpha under the 4-mg dose than was present under either the 2-mg dose or placebo (Table 74). The significant session effect was obtained because of increased alpha from the noon to the evening session.

Table 72.

Contrasts for dose X session interaction for EEG: O_2 , theta.

=====			
	Contrast	F	p

	0 mg-2 mg	9.19	0.0126
Dose at	0 mg-4 mg	32.14	0.0002
noon	2 mg-4 mg	19.84	0.0012
=====			

Table 73.

Contrasts for dose effect for EEG: O_2 , theta.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	12.65	0.0052
	2 mg-4 mg	10.82	0.0080
=====			

Table 74.

Contrasts for dose effect for EEG: O_2 , alpha.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	20.87	0.0010
	2 mg-4 mg	9.83	0.0106
=====			

Beta activity revealed effects due to interactions between dose and session ($F(2,22)=3.82, p=0.0376$) and dose and eyes ($F(2,21)=6.75, p=0.0055$). The dose by session interaction was found to be a result of a tendency toward a dose effect at the noon session ($F(2,21)=3.29, p=0.0573$) which was not observed at the evening session. Subsequent comparisons among dose conditions at noon revealed the effect was a result of substantially lower beta under 4 mg atropine relative to placebo (Table 75). The dose by eyes interaction resulted from a dose effect at eyes-open ($F(2,21)=4.45, p=0.0245$), but not at eyes-closed. Contrasts revealed the effect at eyes-open was due to tendencies toward beta reductions under 2 mg and 4 mg of atropine in comparison to placebo, although both effects were only marginal (Table 76).

Table 75.

Contrasts for dose X session interaction for EEG: O_2 , beta.

	Contrast	F	p
Dose at noon	0 mg-2 mg	NS	
	0 mg-4 mg	5.95	0.0349
	2 mg-4 mg	NS	

Table 76.

Contrasts for dose X eyes interaction for EEG: O_2 , beta.

	Contrast	F	p
Dose with eyes open	0 mg-2 mg	4.48	0.0604
	0 mg-4 mg	4.61	0.0573
	2 mg-4 mg	NS	

The ratio of fast-to-slow activity at O_2 was consistent with the other results. Specifically, there was a dose by session interaction ($F(2,22)=7.43, p=0.0034$) because of a dose effect at noon ($F(2,21)=14.10, p=0.0001$) which did not occur in the evening. The effect was because of decreases in the ratio of

fast to slow activity as the amount of atropine increased (Table 77). Also, there was a main effect on the dose factor ($F(2,21)=9.74$, $p=0.0010$) consistent with what was found in the dose by session interaction except the comparison of 2 mg to placebo did not attain significance (Table 78).

Table 77.

Contrasts for dose X session interaction for EEG: O₂, ratio.

	Contrast	F	p
	0 mg-2 mg	11.94	0.0062
Dose	0 mg-4 mg	18.98	0.0014
at noon	2 mg-4 mg	8.79	0.0142

Table 78.

Contrasts for dose effect for EEG: O₂, ratio.

	Contrast	F	p
	0 mg-2 mg	NS	
Dose	0 mg-4 mg	15.51	0.0028
	2 mg-4 mg	8.48	0.0155

The mean frequency of EEG at O₂ revealed a dose by session interaction ($F(2,22)=7.72$, $p=0.0029$) and a dose effect ($F(2,21)=4.09$, $p=0.0316$). Simple effects explained the two-way interaction by indicating a dose effect at noon ($F(2,21)=6.82$, $p=0.0052$) which was not present at evening. The dose effect at noon was because of substantial reductions in mean frequency under 4 mg as compared to both the 2-mg and placebo doses (Table 79).

The dose effect was completely consistent with the findings reported for the interaction (Table 80). That is, the 4-mg dose was associated with lower frequency activity than were either of the other two doses.

Table 79.

Contrasts for dose X session interaction
for EEG: O₂, mean.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	10.11	0.0098
at noon	2 mg-4 mg	5.55	0.0403
=====			

Table 80.

Contrasts for dose effect for EEG: O₂, mean.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	5.49	0.0358
	2 mg-4 mg	6.66	0.0274
=====			

Summary of EEG findings

All of the above results, taken together, present a clear picture of the impact of atropine on spontaneous EEG. Examination of the interactions across the midline EEG leads showed effects which were fairly well distributed among the different levels of each factor, but the major portion of the interactions themselves were found in the alpha band. The only lead in which the dose by session effect occurred was O₂ where there were differences attributable to dose only in the first postdose session. Significant main effects depicting activity shifts as a function of eyes-open versus eyes-closed were fairly consistent across all leads with the exception of O₂. In every other lead, there was a reduction in both delta and beta activity when eyes were closed, whereas there were no significant effects on theta or alpha activity. The increase in delta under eyes open relative to eyes closed probably resulted from the interdependency among frequency bands. If everything else remained stable from one condition to another with the exception of beta activity, there would appear to be shifts in the amount of activity in the delta and other bands because there is only

100 percent of power to be distributed. The failure to detect significant alpha increases from eyes open to eyes closed came as somewhat of a surprise and was later attributed to an artifact of the analysis of covariance procedure (discussed earlier), especially since increases could be clearly seen in the unadjusted power values. Effects attributable to session alone were not as consistent as the effects attributable to the eyes factor. However, at least F_z , P_z , and O_z leads recorded the lowest overall alpha at the noon session in comparison to the evening session.

Finally, the effects which resulted from the doses revealed the rather reliable effects of atropine on central nervous system activation. The maps of brain activity selected from one subject's eyes-closed condition present a reasonable representation of some of the drug effects which were statistically determined for the whole group (Figures 24 and 25). At every midline electrode except O_z , there was a significant increase in the percentage of delta activity from placebo to 4 mg atropine while the increase from placebo to 2 mg atropine was only observed at F_z . While it is possible part of this delta increase could have been accounted for by eye movements, the fact that it was present under both eyes-open and eyes-closed helps to alleviate this

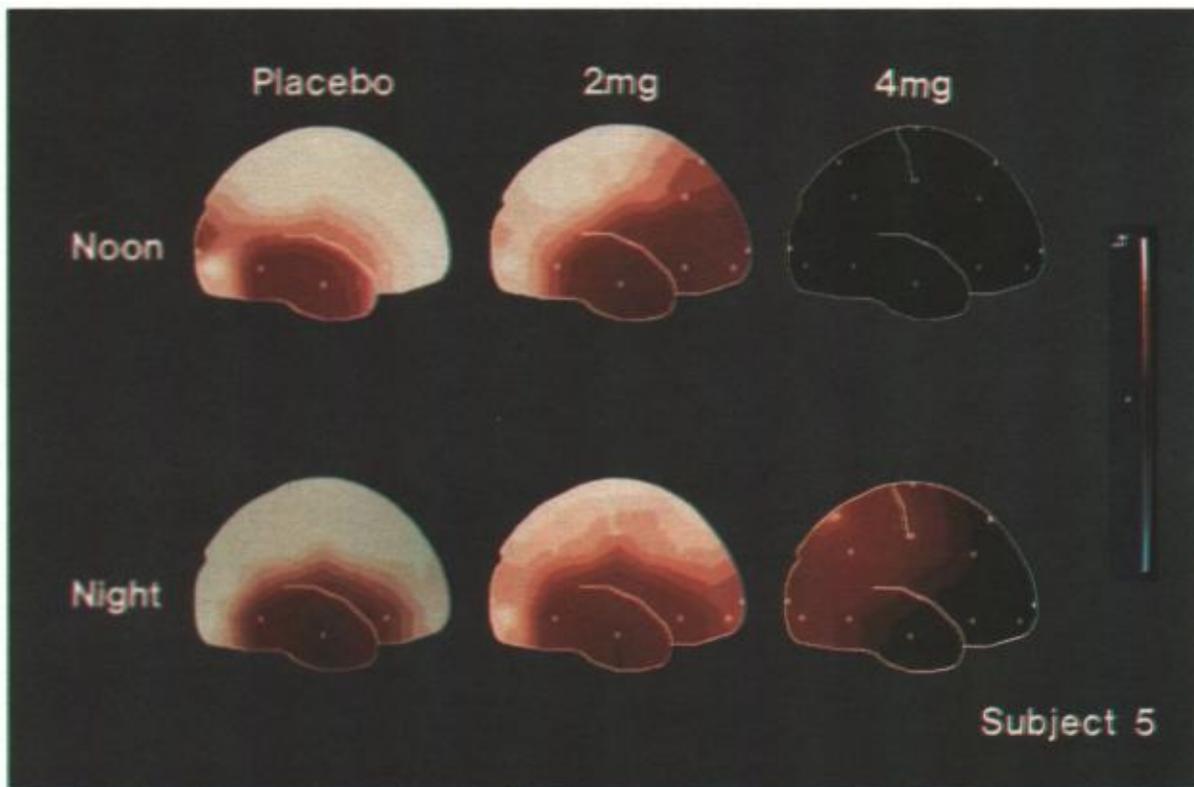


Figure 24. Alpha activity.

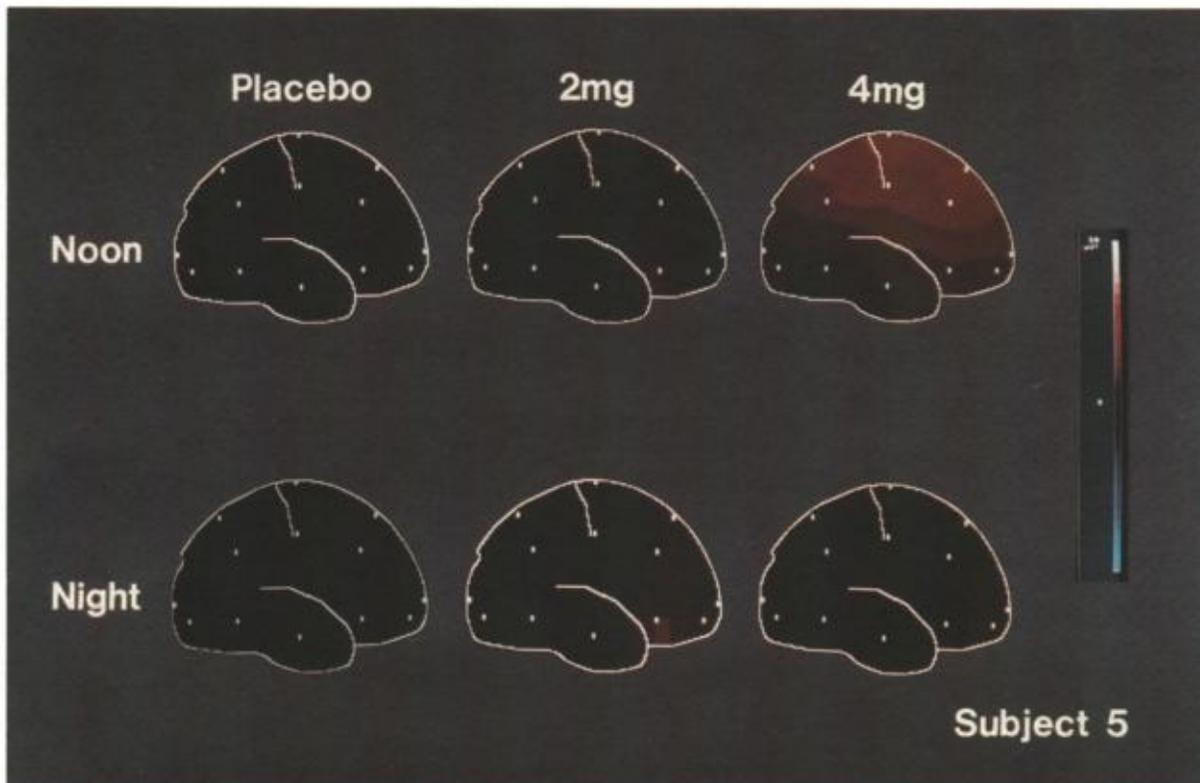


Figure 25. Delta activity.

concern. At both P_2 and O_2 , there also were increases in theta from placebo and 2 mg to 4 mg atropine. Alpha activity was reduced under the 4-mg dose at every single electrode as was the ratio of fast-to-slow activity. The mean frequency shifted to its lowest level under 4 mg at both the parietal and occipital leads. Thus, it may be concluded, at least the 4-mg dose of atropine is associated with a general slowing of EEG activity which is thought to reflect a reduction in overall cortical activation.

Event related potentials

Two separate systems were used for eliciting and storing the ERPs. The Cadwell Spectrum 32 was used to collect the early-component (N75 and P100) evoked responses, and the Cadwell 7400 was used to collect the later-component (P300) data. The waveforms for all components were collected on their respective machines at each of the three sessions for each day of testing. Latencies (in milliseconds) and amplitudes (in microvolts) subsequently were determined, via visual inspection, and then stored for later analysis. The amplitudes of the N75 and P100 peaks were scored from zero, using the channel center marker as a reference. The amplitude of P300 was scored from a visually-

determined baseline estimated from approximately the first 50 ms of the wave (there was no prestimulus baseline). Analyses of covariance were conducted on both the amplitude and latency measures for each peak.

One set of analyses was conducted on the checksizes ranging from 4x4 to 64x64 squares because that was the only series of stimuli to which all 12 subjects were exposed. An additional set of analyses was conducted on the 128x128 checksize data because the first subject used in the protocol was not exposed to this stimulus set (the 128x128 checksize was initially unavailable on the Spectrum 32). For both sets of analyses, one subject was excluded because descriptive statistics indicated he was an "outlier"; and two other subjects were excluded because their data were not always scored due to extraneous "noise."

Early-component (N75 and P100) ERP

For the N75 and P100 components, four separate 3x2x5 repeated-measures analyses of covariance were performed for the amplitudes and latencies as a function of dose, session, and checksize (4x4, 8x8, 16x16, 32x32, 64x64). Morning scores on each dose day served as the covariate for the noon and evening scores on the respective days. The adjusted means are presented in Table 81.

Table 81.

Adjusted means for 4x4 through 64x64 checks.

	2 mg		4 mg		Placebo	
	Noon	Evening	Noon	Evening	Noon	Evening
N75						
Amplitude	-1.6733	-2.4033	-1.0573	-2.3215	-2.2033	-2.2686
Latency	74.5450	71.9866	74.3404	71.8486	74.8395	73.0004
P100						
Amplitude	4.3849	5.2655	4.8134	5.9664	4.3189	4.4664
Latency	100.5809	99.4725	99.5512	100.1612	101.9592	102.2361

Amplitude of N75 component: 4 through 64 checks

Results of the analysis for the N75 amplitudes revealed a dose by checksize interaction ($F(8,63)=2.13$, $p=0.0462$), a dose effect ($F(2,15)=5.09$, $p=0.0205$), a session effect ($F(1,8)=16.15$, $p=0.0038$), and a checksize effect ($F(2.02,15.66)=4.19$, $p=0.0079$). Simple effects for the dose by checksize interaction indicated checksize effects at placebo ($F(4,31)=5.83$, $p=0.0013$), but not at 2 mg or 4 mg of atropine. Subsequent contrasts revealed there were larger N75 components to the 4x4 checks than there were to 8x8, 16x16, 32x32, or 64x64 checks. Also, the amplitude in response to the 8x8 pattern was larger than the amplitude in response to the 32x32 check pattern (Table 82). Apparently, these effects were suppressed by either dose of atropine.

Table 82.

Contrasts for checksize effect at placebo for N75 amplitude.

=====				
Contrast			F	p

Chk	4-chk	8	8.23	0.0240
Chk	4-chk	16	12.24	0.0100
Chk	4-chk	32	15.39	0.0057
Chk	4-chk	64	8.01	0.0254
Chk	8-chk	16		NS
Chk	8-chk	32	31.20	0.0008
Chk	8-chk	64		NS
Chk	16-chk	32		NS
Chk	16-chk	64		NS
Chk	32-chk	64		NS
=====				

The dose main effect was found to be due to N75 amplitude reductions under the 4-mg dose as compared to the 2-mg dose (Table 83). The comparison of 4 mg to placebo, however, was not significant even though the mean amplitude under placebo appeared greater than those under the other conditions (Figure 26).

The session effect was due to smaller N75 amplitudes at noon, when drug levels were highest, than in the evening. The checksize main effect was attributable to amplitude changes quite similar to those seen earlier in the placebo condition when considering the dose by checksize interaction (all means are presented in Table 84).

Table 83.

Contrasts for dose effect for N75 amplitude.

Contrast	F	p
0 mg-2 mg		NS
0 mg-4 mg		NS
2 mg-4 mg	5.58	0.0502

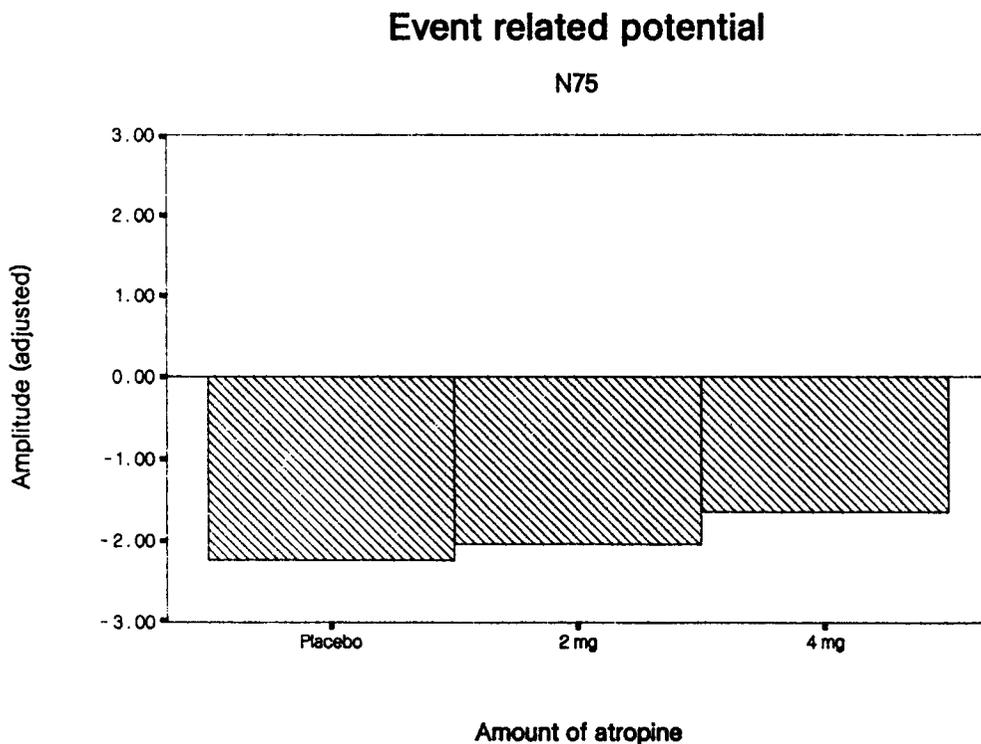


Figure 26. Amplitude of N75 component of event related potential.

Latency of N75 component: 4 through 64 checks

The results of the analysis of covariance for N75 latency revealed a checksize effect ($F(1.66, 12.40) = 4.76, p = 0.0332$) and a session effect ($F(1, 8) = 29.85, p = 0.0006$). The session effect was because of longer latencies at noon than in the evening. The

Table 84.

Means for dose by checksize interaction
and checksize main effect for N75 amplitude.

Checksize	Placebo	2 mg	4 mg	All doses
4	-2.9265	-2.4588	-1.9588	-2.4480
8	-2.3353	-2.0146	-2.1683	-2.1727
16	-2.0512	-1.8560	-1.7322	-1.8798
32	-1.4601	-1.9783	-1.5173	-1.6519
64	-2.4070	-1.8841	-1.0705	-1.7872

checksize effect was due to generally longer latencies with increasing check pattern complexity. Contrasts revealed significant increases in latency to the 64x64 pattern as compared to the 4x4, 8x8, or 16x16 patterns. Also, there were longer latencies in response to the 16x16 pattern than to the 4x4 or 8x8 patterns (see Table 85).

Table 85.

Contrasts for checksize effect for N75 latency.

Contrast	F	p
Chk 4-chk 8		NS
Chk 4-chk 16	24.73	0.0016
Chk 4-chk 32		NS
Chk 4-chk 64	19.27	0.0032
Chk 8-chk 16	42.95	0.0003
Chk 8-chk 32		NS
Chk 8-chk 64	9.32	0.0185
Chk 16-chk 32		NS
Chk 16-chk 64	10.79	0.0135
Chk 32-chk 64		NS

Amplitude of P100 component: 4 through 64 checks

Results of the 3x2x5 repeated-measures analysis of covariance for P100 amplitude revealed a dose by session interaction ($F(2,16)=4.24$, $p=0.0333$), a dose effect ($F(2,15)=9.77$, $p=0.0019$), and a session effect ($F(1,8)=28.58$, $p=0.0007$). Simple effects for the dose by session interaction revealed a session effect at 2 mg of atropine ($F(1,8)=16.65$, $p=0.0035$) and a session effect at 4 mg of atropine ($F(1,8)=10.40$, $p=0.0121$), both attributed to smaller amplitudes at the noon session than at the evening session. Additionally, the simple effects for the dose by session interaction revealed a dose effect at evening ($F(2,15)=19.11$, $p=0.0001$), but not at noon (Figure 27). Contrasts indicated that in the evening, 4 mg of atropine increased P100 amplitude when compared to placebo and 2 mg of atropine (Table 86). Also, 2 mg of atropine increased the P100 amplitude relative to placebo.

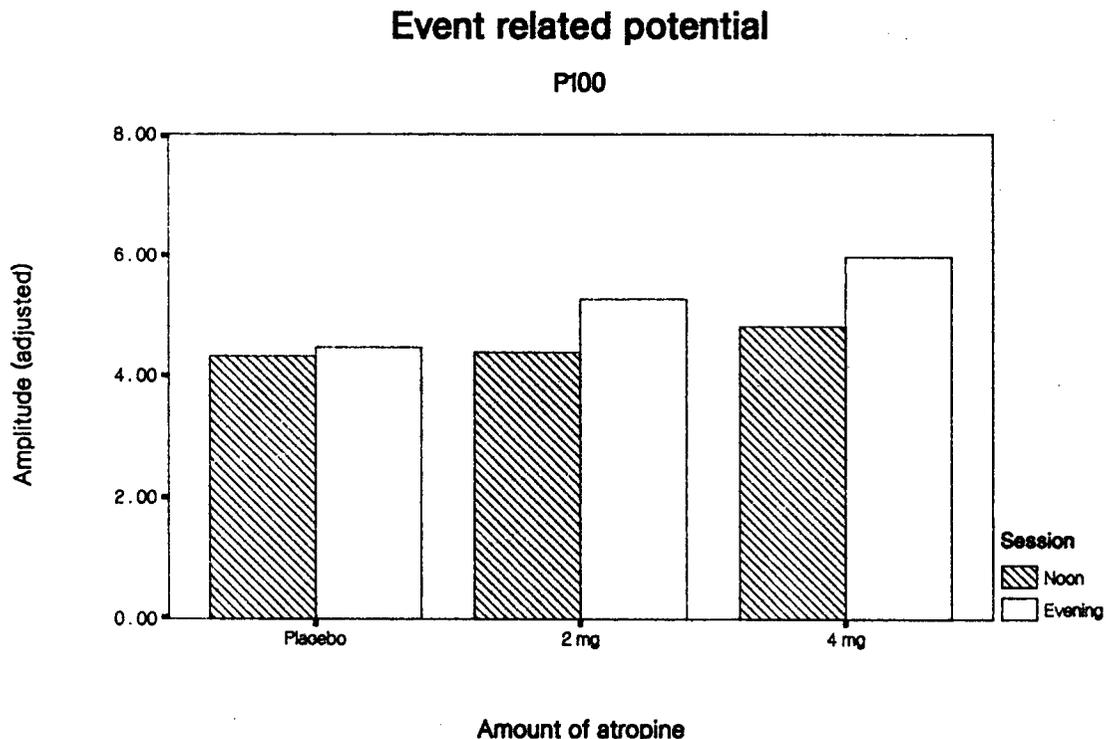


Figure 27. Amplitude of P100 component of event related potential.

The dose main effect for P100 amplitude essentially was identical to what would have been expected based on an analysis of the earlier dose by session interaction in that 4 mg of atropine increased P100 amplitude in comparison to placebo and 2

mg of atropine (Table 87). The session effect indicated subjects showed an increase in P100 amplitude from the noon to evening as was depicted in the N75 data as well.

Table 86.

Contrasts for dose x session interaction for P100 amplitude.

=====			
	Contrasts	F	p

Dose in	0 mg-2 mg	15.60	0.0055
evening	0 mg-4 mg	23.43	0.0019
	2 mg-4 mg	18.60	0.0038
=====			

Table 87.

Contrasts for dose effect for P100 amplitude.

=====			
	Contrasts	F	p

	0 mg-2 mg	NS	
	0 mg-4 mg	10.98	0.0129
	2 mg-4 mg	21.63	0.0023
=====			

Latency of P100 component: 4 through 64 checks

The results of the analysis of covariance for P100 latency revealed only a checksize effect ($F(2.12,16.41)=4.44$, $p=0.0270$) due to significant latency reductions in response to the 4x4 pattern as compared to the 8x8, 16x16, and 32x32 patterns. Curiously, there was no difference between the 4x4- and the 64x64-check patterns (Table 88).

Amplitudes and latencies of N75 and P100 components: 128 checks

For the 128x128 checksizes, separate 3x2 repeated-measures analyses of covariance were performed for the amplitude and latency values for N75 and P100 components. Morning scores on each dose day served as the covariate for the noon and evening

scores on the respective days in the same manner in which all the preceding data were analyzed. The means are presented in Table 89.

Table 88.

Contrasts for checksize effect for P100 latency.

Contrast			F	p
Chk	4-chk	8	9.33	0.0184
Chk	4-chk	16	6.71	0.0360
Chk	4-chk	32	10.70	0.0136
Chk	4-chk	64		NS
Chk	8-chk	16		NS
Chk	8-chk	32		NS
Chk	8-chk	64		NS
Chk	16-chk	32		NS
Chk	16-chk	64		NS
Chk	32-chk	64		NS

Table 89.

Adjusted means for 128x128 checks.

	2 mg		4 mg		Placebo	
	Noon	Evening	Noon	Evening	Noon	Evening
N75						
Amplitude	-1.7601	-3.4164	-0.8795	-2.8745	-4.3054	-4.1879
Latency	81.7246	82.3508	74.8997	81.7547	88.0144	88.9482
P100						
Amplitude	2.3094	3.2007	2.1189	2.2576	3.3204	3.1029
Latency	107.8803	110.3716	95.9607	106.2420	121.1840	121.1864

Results of the analysis for the N75 amplitude revealed a dose effect ($F(2,13)=6.49$, $p=0.0111$) and a session effect ($F(1,7)=15.01$, $p=0.0061$). Contrasts for the dose effect indicated a reduction in amplitude only when 4 mg of atropine was compared to the placebo condition (Table 90). The session effect

was because of smaller amplitudes at the noon session than at the evening session.

Table 90.

Contrasts for dose effect for N75 amplitude (128x128 checksize).

Contrast	F	p
0 mg-2 mg		NS
0 mg-4 mg	9.12	0.0234
2 mg-4 mg		NS

Analyses for the N75 latency and the P100 amplitude and latency for the 128x128 check pattern revealed no significant main effects or interactions.

Amplitude and latency of late component ERP (P300)

The P300 data for both amplitude and latency were analyzed with a 3x2 repeated measures analysis of covariance with the usual three levels of dose and two levels of session. Once again, the morning score for each variable was used as the covariate for noon and evening scores collected on the same dose-administration day. Data of three subjects were eliminated from the analysis: two because of noise artifact; one because of missing data due to equipment malfunction. These data were generally somewhat noisier (more 60 Hz) than one would have hoped for, probably because of the installation of some high voltage electrical lines nearby; however, the P300 was scored.

Results of this analysis for P300 amplitudes revealed no interactions, but a significant dose effect ($F(2,15)=3.76$, $p=0.0474$). Contrasts indicated 4 mg of atropine decreased P300 amplitude when compared to 2 mg (Table 91).

Results of this analysis for P300 latencies revealed a session effect ($F(1,8)=7.48$, $p=0.0257$) and a dose effect ($F(2,15)=5.79$, $p=0.0137$). The session effect was due to an increase in latency during the noon session relative to the evening session. Contrasts among the doses indicated 4 mg of atropine increased P300 latency when compared to either placebo or 2 mg of atropine (Table 92).

Table 91.

Contrasts for dose effect for P300 amplitude.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg		NS
	2 mg-4 mg	14.42	0.0067
=====			

Table 92.

Contrasts for dose effect for P300 latencies.

=====			
	Contrast	F	p

	0 mg-2 mg		NS
Dose	0 mg-4 mg	13.85	0.0074
	2 mg-4 mg	12.03	0.0104
=====			

Performance assessment battery

Prior to analysis, data from two of the five PAB tests were classified on the basis of the stimulus category of the trial which elicited the response. Data from the 6-letter search task were classified according to whether all 6 letters of the target string were present in or absent from the 20-letter search string. This resulted in two stimulus categories: stimulus absent and stimulus present. Data from the logical reasoning task were classified according to whether or not the sentence describing the letter pair contained a negation and whether it was worded in the active or passive voice. This resulted in four stimulus categories for logical reasoning: negation absent-active voice, negation absent-passive voice, negation present-active voice, and negation present-passive voice. An attempt was made to classify data from the serial addition/subtraction task also. However, due to an unequal number of trials at each of the item types, summary data were subject to the influence of chance fluctuations in performance. The digit recall and four-choice serial reaction time (RT) tasks did not provide relevant

dimensions for classification of data based on stimulus conditions.

The raw data from each trial for the six-letter search and logical reasoning tasks were sorted according to stimulus category, and summary statistics were calculated for each stimulus category. Summary statistics for the remaining three tasks were generated across all trials. Data then were submitted to analyses using the following four measures from each of the five PAB tasks: 1) mean RT for correct responses (sec), 2) percent correct, 3) speed (total number of responses per minute), and 4) throughput (number of correct responses per minute). Following selection of the dependent variable set, data from all 12 subjects were first analyzed to determine whether any changes occurred across successive sessions due to continued practice (i.e., training effects). Such changes in baseline performance were assessed by submitting data from the morning (predose) sessions of successive days to repeated measures analysis of variance using orthogonal polynomial decomposition for trend analysis.

Results of this analysis indicated stable baseline performance was not obtained prior to administration of the first dose for a majority of the measures. Therefore, subsequent analysis of atropine effects was performed using analysis of covariance with the morning (predose) session score serving as the covariate for the corresponding noon and evening sessions.

For the six-letter search and logical reasoning tasks, these analyses were three-way factorial analyses of covariance with repeated measures on dose (placebo, 2 mg, and 4 mg), session (noon and evening), and stimulus type (levels varied for each task). For the digit recall, serial addition/subtraction, and four-choice serial RT tasks, the analyses were identical except that stimulus type was not included as a factor. Results will be discussed for each task separately.

Six-letter search

There were no three-way interactions for any of the measures for the six-letter search task. However, two-way interactions between dose and stimulus type were detected on mean RT for correct responses ($F(2,21)=6.37$, $p=0.0069$) and speed ($F(2,21)=5.75$, $p=0.0102$). None of the other two-way interactions were significant.

Analysis of simple effects for the dose by stimulus type interaction on mean RT for correct responses is portrayed in Figure 28. It indicated significant stimulus type effects at placebo ($F(1,10)=6.33$, $p=0.0306$), 2 mg ($F(1,10)=6.64$, $p=0.0276$),

and 4 mg ($F(1,10)=15.73$, $p=0.0027$). In each case, RTs in the stimulus absent condition were shorter than those in the stimulus present condition.

Six-letter search

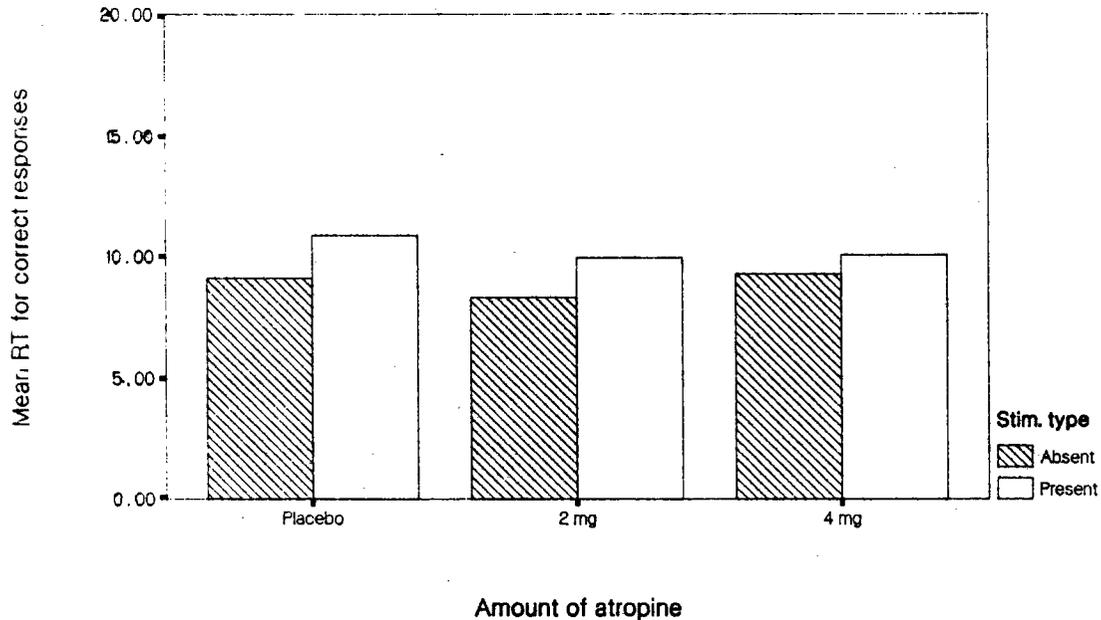


Figure 28. Dose by stimulus type interaction on mean RT for correct responses to six-letter search task.

Analysis of simple effects for the dose by stimulus type interaction on speed revealed a dose effect at the absent condition ($F(2,21)=3.41$, $p=0.0524$) due to a significant decrease in speed of responding under the 4-mg dose compared to the 2-mg dose (Table 93). Also, while not significant, there was a tendency toward faster responding under 2 mg of atropine compared to placebo (Figure 29).

Finally, there was a stimulus type effect on the mean RT for correct responses for this task ($F(1,10)=7.39$, $p=0.0216$). Regardless of dose, the mean RT was faster for the stimulus absent trials than for stimulus present trials.

Table 93.

Contrasts for the dose x stimulus interaction
in the six-letter search task: Speed.

	Contrast	F	p
Dose	0 mg - 2 mg		NS
at absent	0 mg - 4 mg		NS
	2 mg - 4 mg	8.52	0.0048

Six-letter search

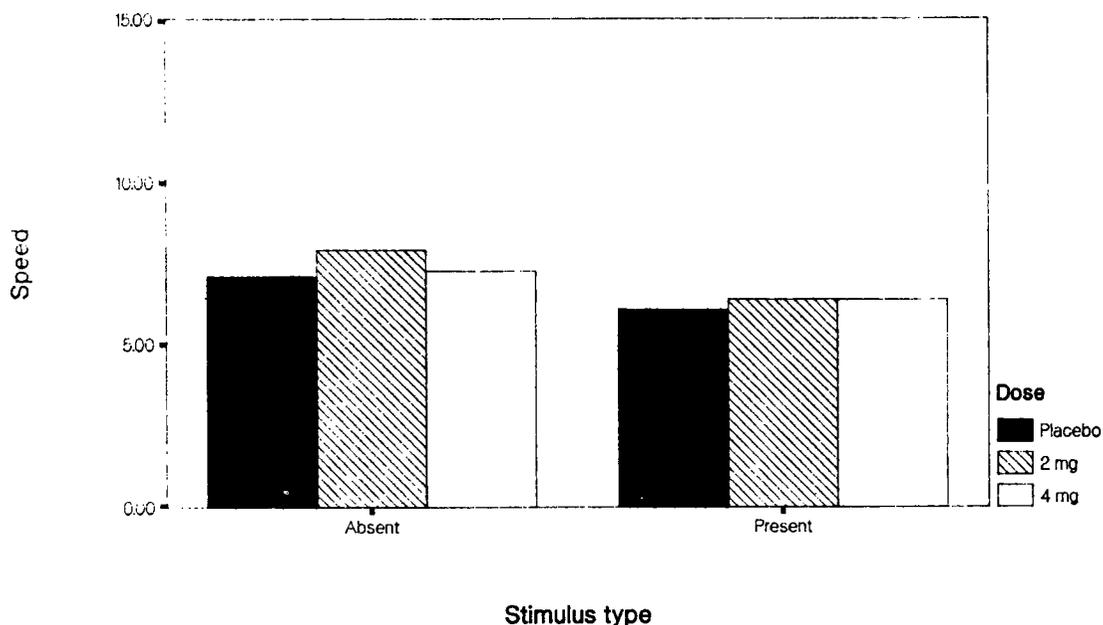


Figure 29. Dose by stimulus type interaction on speed of six-letter search.

Logical reasoning

Analyses for the four measures on the logical reasoning task indicated there were no three-way interactions. Two-way interactions existed between dose and session for percent correct ($F(2,22)=4.68, p=0.0203$), and between dose and stimulus type for

speed ($F(3.2,34.6)=3.95$, $p=0.0144$) and throughput ($F(6,65)=5.28$, $p=0.0002$).

Analysis of simple effects on the dose by session interaction for percent correct, shown in Figure 30, revealed dose effects at the noon session ($F(2,21)=4.83$, $p=0.0188$) and at the evening session ($F(2,21)=3.89$, $p=0.0366$). Contrasts for the dose effect at noon indicated 4 mg of atropine decreased accuracy of performance when compared to placebo. Neither of the other contrasts was significant. Contrasts for the dose effect at evening suggested performance under the 4-mg dose had recovered to the extent accuracy was increased relative to the 2-mg dose. The placebo condition did not differ significantly from either the 2-mg or the 4-mg conditions (Table 94).

Logical reasoning

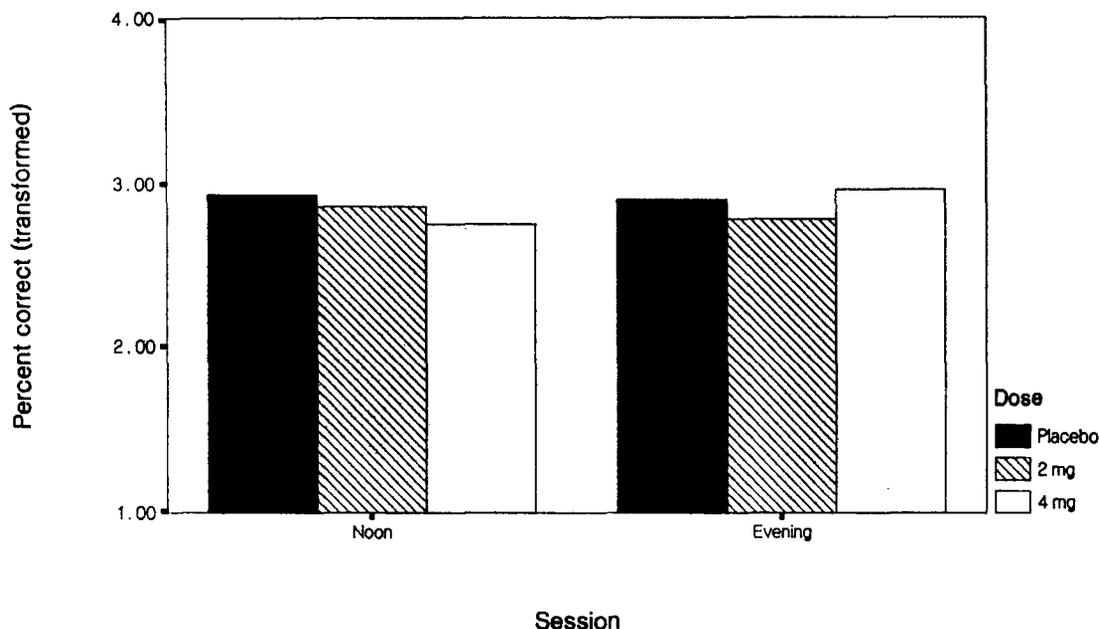


Figure 30. Dose by session interaction for percent correct in logical reasoning task.

Analysis of simple effects on the dose by stimulus type interaction for speed, shown in Figure 31, revealed a dose effect only at the negation absent-active voice condition ($F(2,21)=6.48$, $p=0.0064$). Furthermore, there were stimulus type effects at placebo ($F(3,32)=4.36$, $p=0.0110$), 2 mg ($F(3,32)=2.99$, $p=0.0453$), and 4 mg ($F(3,32)=4.07$, $p=0.0147$).

Table 94.

Contrasts for the dose x session interaction in the logical reasoning task: Percent correct (transformed).

	Contrast	F	p
Dose at noon	0 mg - 2 mg		NS
	0 mg - 4 mg	9.27	0.0124
	2 mg - 4 mg		NS
Dose in evening	0 mg - 2 mg		NS
	0 mg - 4 mg		NS
	2 mg - 4 mg	11.25	0.0073

Logical reasoning

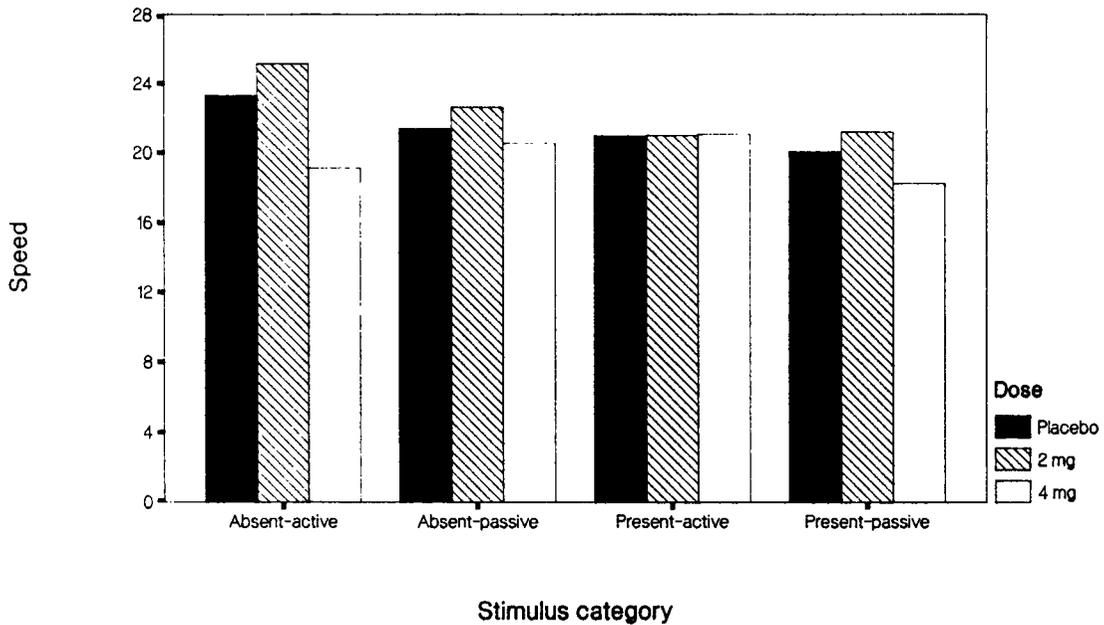


Figure 31. Dose by stimulus type interaction for speed in logical reasoning task.

Contrasts for the dose effect at negation absent-active voice indicated 4 mg of atropine reduced the speed of responding relative to both 2 mg of atropine and placebo. While not

significant, there was a tendency toward faster responding under 2 mg of atropine compared to placebo (top section of Table 95).

Table 95.

Contrasts for the dose x stimulus interaction
in the logical reasoning task: Speed.

		Contrast	F	p
=====				
Dose at		0 mg - 2 mg		NS
NA AV		0 mg - 4 mg	8.18	0.0170
		2 mg - 4 mg	6.63	0.0276
=====				
Stimulus at		NA AV - NA PV		NS
		NA AV - NP AV		NS
placebo		NA AV - NP PV		NS
		NA PV - NP AV		NS
		NA PV - NP PV		NS
		NP AV - NP PV	8.87	0.0138

Stimulus		NA AV - NA PV	5.45	0.0417
		NA AV - NP AV	5.37	0.0429
at 2 mg		NA AV - NP PV		NS
		NA PV - NP AV	6.06	0.0335
		NA PV - NP PV		NS
		NP AV - NP PV		NS

Stimulus		NA AV - NA PV		NS
		NA AV - NP AV	5.30	0.0441
at 4 mg		NA AV - NP PV		NS
		NA PV - NP AV		NS
		NA PV - NP PV		NS
		NP AV - NP PV	9.16	0.0128
=====				

The stimulus effect at placebo was due to a reduction in the speed of responding for passive voice trials compared to active voice trials only when a negation was present in the sentence describing the letter pair. Contrasts for the stimulus effect at 2 mg indicated subjects responded faster in the negation absent-active voice condition than in either the negation absent-passive voice condition or the negation present-active voice condition. Furthermore, subjects responded faster on the negation absent-

passive voice trials than on the negation present-active voice trials. The stimulus effect at 4 mg occurred because subjects responded faster on negation present-active voice trials than on either negation absent-active voice trials or negation present-passive voice trials (lower section of Table 95).

Analysis of simple effects on the dose by stimulus type interaction for throughput produced results similar to those for speed (Figure 32). There was a dose effect again only for negation absent-active voice trials ($F(2,21)=7.91, p=0.0028$); and there were stimulus effects at placebo ($F(3,32)=4.38, p=0.0108$), 2 mg ($F(3,32)=3.63, p=0.0231$), and 4 mg ($F(3,32)=5.00, p=0.0059$).

Logical reasoning

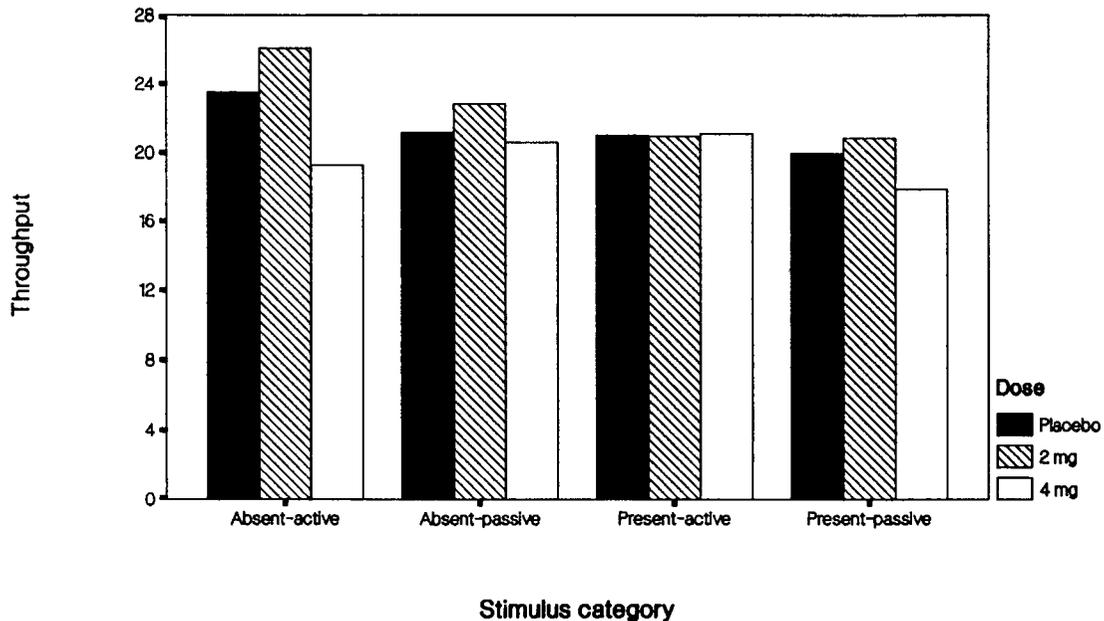


Figure 32. Dose by stimulus type interaction for throughput in logical reasoning task.

Contrasts for the dose effect at negation absent-active voice indicated subjects generated fewer correct responses per minute under 4 mg of atropine than under either placebo or 2 mg of atropine (top section of Table 96). Again there was a tendency for 2 mg of atropine to facilitate the speed of correct responses relative to placebo, but the difference was not significant. The stimulus effect at placebo was a result of the speed of correct responses being reduced for passive voice trials relative to active voice trials only when a negation was present.

Table 96.

Contrasts for the dose x stimulus interaction
in the logical reasoning task: Throughput.

		Contrast	F	p
Dose at		0 mg - 2 mg		NS
	NA AV	0 mg - 4 mg	7.26	0.0226
		2 mg - 4 mg	8.70	0.0146
Stimulus at placebo		NA AV - NA PV		NS
		NA AV - NP AV		NS
		NA AV - NP PV		NS
		NA PV - NP AV		NS
		NA PV - NP PV		NS
		NP AV - NP PV	10.18	0.0096
	Stimulus at 2 mg		NA AV - NA PV	
		NA AV - NP AV	7.65	0.0199
		NA AV - NP PV		NS
		NA PV - NP AV	8.57	0.0151
		NA PV - NP PV		NS
		NP AV - NP PV		NS
Stimulus at 4 mg		NA AV - NA PV		NS
		NA AV - NP AV		NS
		NA AV - NP PV		NS
		NA PV - NP AV		NS
		NA PV - NP PV		NS
		NP AV - NP PV	9.62	0.0112

The stimulus effect at 2 mg was due to a reduction in the number of correct responses per minute in the negation present-active voice condition relative to both of the negation absent conditions. The stimulus effect at 4 mg occurred because throughput was significantly reduced on negation present-passive voice trials relative to negation present-active voice trials (lower section of Table 96).

In addition, the throughput measure exhibited both a dose effect ($F(2,21)=3.73$, $p=0.0410$) and a session effect ($F(1,11)=6.21$, $p=0.0299$). There was a tendency for subjects to exhibit faster throughput under 2 mg of atropine than under

either of the other dosages. The 4-mg dose apparently reduced the number of correct responses per minute relative to the 2-mg dose; however, the contrast for this comparison only approached significance ($p=0.0583$). The session effect was due to an increase in throughput from noon to evening regardless of the amount of atropine administered.

Digit recall

Analyses for the digit recall task indicated there were no significant interactions for any of the measures. Dose effects were detected on percent correct ($F(2,21)=3.68$, $p=0.0428$) and throughput ($F(2,21)=4.20$, $p=0.0292$). No other significant effects were observed.

Examination of the dose effect on percent correct indicated accuracy of recall was reduced by 4 mg of atropine relative to placebo (Table 97). The dose effect on throughput was due to a reduction in the number of correct responses per minute under 4 mg of atropine compared to both placebo and 2 mg of atropine (Table 98).

Table 97.

Contrasts for the dose effect in the digit recall task:
Percent correct (transformed).

	Contrast	F	p
	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	9.61	0.0112
	2 mg - 4 mg		NS

Serial addition/subtraction

As noted earlier, analyses for this task involved two-way analyses of covariance with repeated measures on each of the two factors (dose and session). A dose by session interaction was not detected on any of the dependent variables for this task. However, dose effects were observed on mean RT for correct responses ($F(2,21)=9.41$, $p=0.0012$), speed ($F(2,21)=8.05$, $p=0.0025$), and throughput ($F(2,21)=7.22$, $p=0.0041$). Session effects were detected on each of these measures as well: mean RT for correct responses ($F(1,11)=11.37$, $p=0.0062$), speed

($F(1,11)=5.20$, $p=0.0436$), and throughput ($F(1,11)=5.59$, $p=0.0375$). In each case, the session effect was a result of improved performance in the evening relative to the noon session.

Table 98.

Contrasts for the dose effect in the digit recall task:
Throughput.

=====			
	Contrast	F	p

	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	8.89	0.0138
	2 mg - 4 mg	5.09	0.0477
=====			

Contrasts for the dose effect on mean RT for correct responses revealed RTs were longer under 4 mg of atropine than under either placebo or 2 mg of atropine. There was no difference between the placebo and 2-mg conditions (Table 99). The dose effect on speed was similar. The number of trials completed per minute decreased significantly under the influence of 4 mg of atropine when compared to placebo and 2 mg atropine.

Table 99.

Contrasts for the dose effect in the serial addition/subtraction task: Mean RT correct.

=====			
	Contrast	F	p

	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	10.37	0.0092
	2 mg - 4 mg	11.09	0.0076
=====			

Again there was no difference between the placebo and 2-mg conditions (Table 100). The dose effect on throughput indicated the same pattern as found with speed (Table 101).

Table 100.

Contrasts for the dose effect in the serial addition/subtraction task: Speed.

=====			
	Contrast	F	p

	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	11.88	0.0063
	2 mg - 4 mg	10.53	0.0088
=====			

Table 101.

Contrasts for the dose effect in the serial addition/subtraction task: Throughput.

=====			
	Contrast	F	p

	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	9.55	0.0114
	2 mg - 4 mg	9.75	0.0108
=====			

Four-choice serial RT

Analyses for the four-choice serial RT task revealed dose by session interactions on mean RT for correct responses ($F(1.1,12.6)=5.93$, $p=0.0273$), percent correct ($F(2,22)=5.39$, $p=0.0124$), speed ($F(1.3,13.8)=5.48$, $p=0.0286$), and throughput ($F(1.2,13.1)=11.28$, $p=0.0038$).

Analysis of simple effects indicated the dose by session interaction on mean RT for correct responses, as seen in Figure 33, was due in part to session effects at 2 mg ($F(1,11)=12.08$, $p=0.0052$) and 4 mg ($F(1,11)=8.06$, $p=0.0161$). In each case, RTs decreased from the noon session to the evening session. Also, there were dose effects at noon ($F(2,21)=6.79$, $p=0.0053$) and evening ($F(2,21)=4.18$, $p=0.0297$).

Serial RT

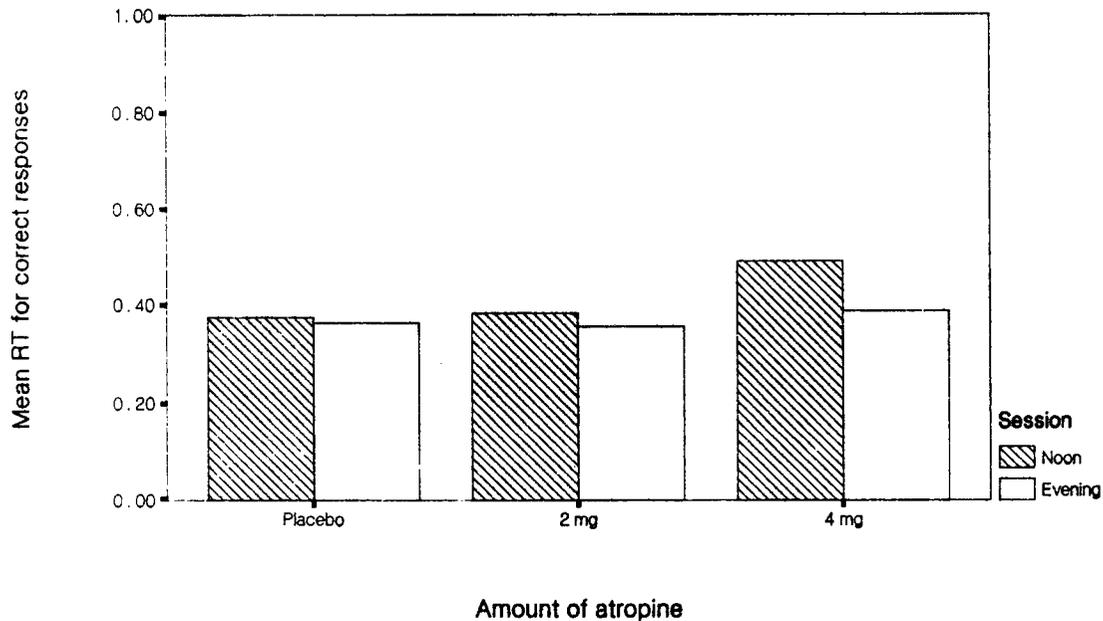


Figure 33. Dose by session interaction on mean RT for correct responses to serial RT task.

Contrasts for the dose effect at noon on mean RT for correct responses indicated 4 mg of atropine increased RTs relative to both placebo and 2 mg of atropine. RTs under placebo and 2 mg of atropine did not differ significantly. Contrasts for the dose effect at the evening session revealed 4 mg of atropine slowed correct responses significantly relative to 2 mg of atropine (Table 102).

Analysis of simple effects on the dose by session interaction for percent correct, displayed in Figure 34, revealed a session effect at 4 mg ($F(1,11)=14.78$, $p=0.0027$) and a dose effect at noon ($F(2,21)=5.08$, $p=0.0159$). The session effect was due to an increase in accuracy of performance from the noon session to the evening session under 4 mg of atropine. Contrasts for the dose effect at the noon session indicated a significant decrease in accuracy under 4 mg of atropine relative to placebo (Table 103).

Analysis of simple effects for the dose by session interaction for speed, illustrated in Figure 35, revealed session effects at both 2 mg ($F(1,11)=25.43$, $p=0.0004$) and 4 mg ($F(1,11)=16.03$, $p=0.0021$). In both cases, speed increased from the noon session to the evening session. In addition, there were

dose effects at both the noon session ($F(2,21)=13.66$, $p=0.0002$) and the evening session ($F(2,21)=7.01$, $p=0.0047$).

Table 102.

Contrasts for the dose x session interaction in the four-choice RT task: Mean RT correct.

	Contrast	F	p
Dose at noon	0 mg - 2 mg	NS	
	0 mg - 4 mg	7.55	0.0206
	2 mg - 4 mg	6.46	0.0293
Dose in evening	0 mg - 2 mg	NS	
	0 mg - 4 mg	NS	
	2 mg - 4 mg	6.30	0.0309

Serial RT

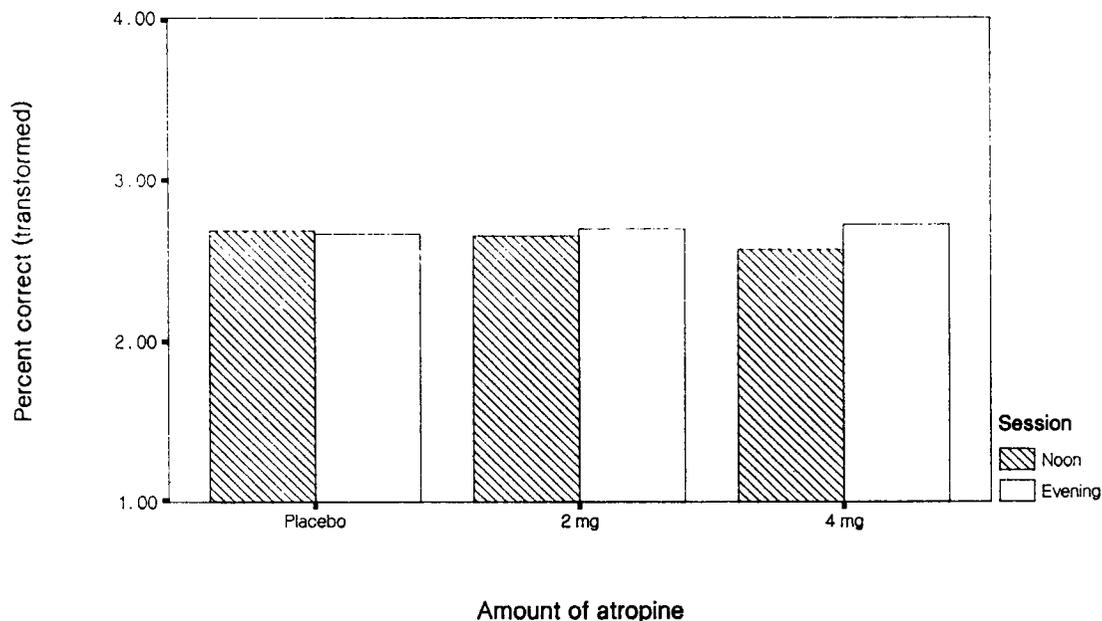


Figure 34. Dose by session interaction on percent correct on serial RT task.

Table 103.

Contrasts for the dose x session interaction in the four-choice RT task: Percent correct (transformed).

Contrast		F	p
Dose	0 mg - 2 mg		NS
at noon	0 mg - 4 mg	8.43	0.0158
	2 mg - 4 mg		NS

Serial RT

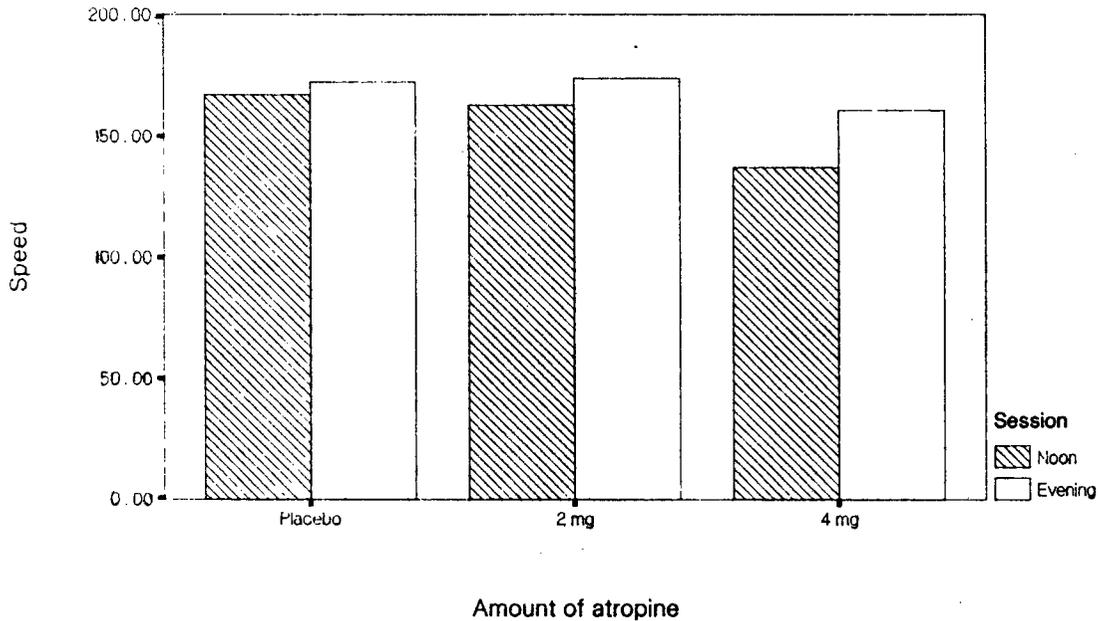


Figure 35. Dose by session interaction on speed of serial RT task.

Contrasts for the dose effect at noon revealed a reduction in the number of items completed per minute in the 4-mg condition when compared to both the placebo and 2-mg conditions. Contrasts for the dose effect at the evening session revealed that while speed increased from noon to evening under both 2 mg and 4 mg of atropine, fewer items were completed per minute during the 4-mg

evening session than during the 2-mg evening session. None of the other contrasts were significant (Table 104).

Table 104.

Contrasts for the dose x session interaction
in the four-choice RT task: Speed.

=====			
	Contrast	F	p

Dose at noon	0 mg - 2 mg		NS
	0 mg - 4 mg	14.37	0.0035
	2 mg - 4 mg	14.23	0.0036

Dose in evening	0 mg - 2 mg		NS
	0 mg - 4 mg		NS
	2 mg - 4 mg	13.41	0.0044
=====			

Analysis of simple effects for the throughput measure as seen in Figure 36 indicated there were session effects at both 2 mg ($F(1,11)=19.36$, $p=0.0011$) and 4 mg ($F(1,11)=20.20$, $p=0.0009$). In both cases, there were increases in the number of correct responses per minute from the noon session to the evening session. Also, there were dose effects at both noon ($F(2,21)=13.78$, $p=0.0002$) and evening ($F(2,21)=5.76$, $p=0.0101$). The dose at noon effect was due to 4 mg of atropine decreasing the number of correct responses per minute relative to both placebo and 2 mg. The dose in evening effect was similar to that for speed. Only the difference between 2 mg and 4 mg atropine was significant (Table 105).

In addition to the dose by session interactions, analysis of covariance revealed dose and session main effects. Dose effects were found on the mean RT for correct responses ($F(1.3,13.7)=6.90$, $p=0.0150$), speed ($F(2,21)=16.64$, $p<0.0001$), and throughput ($F(2,21)=12.93$, $p=0.0002$). In each case, 4 mg of atropine degraded performance relative to both placebo and 2 mg of atropine (Tables 106 through 108).

Session effects were detected on the mean RT for correct responses ($F(1,11)=10.05$, $p=0.0089$), percent correct ($F(1,11)=8.08$, $p=0.0160$), speed ($F(1,11)=31.39$, $p=0.0002$), and throughput ($F(1,11)=26.26$, $p=0.0003$), because of improved performance from the noon session to the evening session.

Serial RT

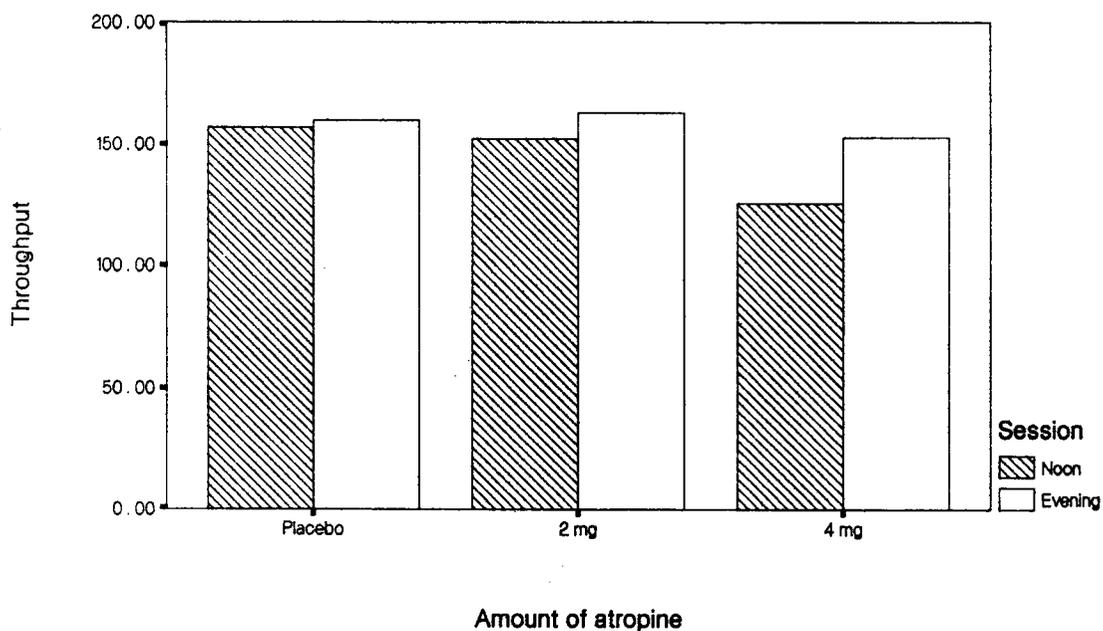


Figure 36. Dose by session interaction on throughput of serial RT task.

Table 105.

Contrasts for the dose x session interaction in the four-choice RT task: Throughput.

	Contrast	F	p
Dose at noon	0 mg - 2 mg		NS
	0 mg - 4 mg	15.94	0.0025
	2 mg - 4 mg	12.53	0.0054
Dose in evening	0 mg - 2 mg		NS
	0 mg - 4 mg		NS
	2 mg - 4 mg	8.93	0.0136

Table 106.

Contrasts for the dose effect in the four-choice RT task:
Mean RT correct.

Contrast		F	p
	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	7.37	0.0217
	2 mg - 4 mg	6.87	0.0255

Table 107.

Contrasts for the dose effect in the four-choice RT task:
Speed.

Contrast		F	p
	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	17.01	0.0021
	2 mg - 4 mg	19.48	0.0013

Table 108.

Contrasts for the dose effect in the four-choice RT task:
Throughput.

Contrast		F	p
	0 mg - 2 mg		NS
Dose	0 mg - 4 mg	14.74	0.0033
	2 mg - 4 mg	12.99	0.0048

Zero input tracking analyzer

Four dependent variables were used for the ZITA data analysis: 1) the primary tracking score, 2) the total number of auxiliary distraction task (ADT) tones responded to expressed as a percent of the total number presented, 3) the percentage of correct responses out of the total number responded to, and 4) the number of tones missed (not responded to). The latter three variables were derived from the responses to the secondary (distraction) task when this secondary task was used. The tracking score was a computer-generated number which ranged from 0 to 9999. It measured the time integration of the absolute distance of the tracking spot from the target. The lower the score, the better the tracking. A score of 0 represented perfect performance, while a score of 1000 represented an average deflection of 1 cm for 30 seconds (Norman K. Walker Associates, Inc., n.d.). Before analysis, the percentage of correct responses was transformed using the arcsin transformation discussed earlier. The number of missed responses was examined with measures of association and log-linear model-building capabilities from the frequency tables program, found in BMDP4F (Dixon et al., 1983) because analysis of variance was inappropriate.

Examination of plots of the log mean versus the log standard deviation of scores for each of the task/ADT combinations suggested scores produced under the differing demands of the three tracking tasks should not be analyzed together because of large differences in the patterns of variability (Table 109). Thus, each of the tasks was analyzed separately.

Table 109.

Standard deviations of tracking scores for ZITA.

D o s e	A D T	Task 1			Task 2			Task 3		
		Session			Session			Session		
		Morn	Noon	Eve	Morn	Noon	Eve	Morn	Noon	Eve
0	0	13	18	21	77	104	58	1466	836	1706
	2	30	46	26	183	183	180	2067	2012	1459
	1	47	54	41	394	345	325	1453	2468	1570
2	0	19	24	20	97	82	60	1561	1042	1652
	2	29	31	24	92	113	97	1614	1327	1545
	1	36	43	50	215	224	108	1823	1573	1316
4	0	34	68	22	75	708	83	1664	2109	1472
	2	21	122	27	268	1178	161	1816	2502	1613
	1	22	154	39	519	1520	246	1366	1947	2193

Before beginning the final analyses, the data were examined for what appeared to be an independently organized improvement in tracking scores over the testing period, as was done with the performance assessment battery data. Since the morning session of each day was drug-free, the scores for that session were first examined across days to determine whether or not there was a trend, such as might be generated by practice, that could account for some of the observed variance in the noon and evening sessions. For each of the nine task/ADT combinations, an analysis of variance was performed to show the orthogonal decomposition of the factor concerned with these day-to-day effects. Each combination revealed a statistically significant day effect; and, in each one, only the linear trend was statistically significant.

To correct for the "practice" effects, the noon and evening scores for each dose day were analyzed by using the respective morning score as a covariate. Thus, the analysis performed on the tracking scores was a 3 x 2 x 3 analysis of covariance with repeated measures on each of three factors: dose (placebo, 2 mg, and 4 mg), session (noon and evening), and ADT (0, 2, and 1). With regard to defining the levels of ADT, the presentation of no tones was labelled ADT0, the presentation of 1 tone every 2 seconds was labelled ADT2, and the presentation of 1 tone every second was labelled ADT1. For the measures of percent responded to out of total presented and percent correct out of total responded to, a 3 x 2 x 2 analysis of covariance with repeated measures on each of the same three factors (dose, session, and ADT) was used. In this case, however, ADT0 was not included. For the frequency examination of the number of tones missed, all three sessions were examined in the analysis rather than using the morning session as a covariate. For these analyses, any ADT effects were disregarded because of the inherent differences in number of tones presented in the ADT1 and ADT2 conditions.

Task 1

Tracking score

The only statistically significant interaction observed for the tracking score in task 1 involved dose and ADT ($F(2,18,23.47)=3.63, p=0.0389$). Examination of simple effects revealed the differences between levels of ADT were significant only at the 4-mg dose ($F(2,21)=8.98, p=0.0015$), while the dose effect was significant at all three levels of ADT ($F(2,21)=5.40, p=0.0128$; $F(2,21)=4.73, p=0.0201$; and $F(2,21)=7.40, p=0.0037$ for ADT0, ADT2, and ADT1, respectively). Contrasts performed on the adjusted means (Table 110) of the three levels of ADT at 4 mg indicated performance was better with ADT0 than with either ADT2 or ADT1, while the difference between ADT2 and ADT1 maintained

Table 110.

Adjusted means of scores for dose X ADT interaction
for ZITA, task 1.

Dose	0 mg	2 mg	4 mg
ADT0	94.5	83.0	104.5
ADT2	94.0	88.5	132.0
ADT1	94.5	94.5	162.0

the same pattern, but only approached significance (top of Table 111). Contrasts for the three dose conditions at each level of ADT revealed the difference between the placebo and 2-mg conditions was not significant at any level of ADT; however, performance under 4 mg was poorer than performance under placebo for ADT2 and ADT1 (bottom of Table 111). Performance under 4 mg of atropine was poorer than performance under 2 mg for ADT0 and ADT1.

Table 111.

Contrasts for dose X ADT interactions for scores on ZITA, task 1.

	ADT0-ADT2		Contrast ADT0-ADT1		ADT2-ADT1	
	F	p	F	p	F	p
ADT at 4 mg	5.14	0.0468	11.53	0.0068	4.56	0.0585

	Placebo-2 mg		Placebo-4 mg		2 mg-4 mg	
	F	p	F	p	F	p
Dose at ADT0	NS		NS		7.11	0.0237
Dose at ADT2	NS		5.98	0.0356	NS	
Dose at ADT1	NS		7.49	0.0209	7.24	0.0227

Main effects were found on session ($F(1,11)=5.11, p=0.0450$), dose ($F(1.05,10.98)=7.03, p=0.0216$), and ADT ($F(2,21)=3.38, p=0.0533$). With respect to the overall session effect, noon performance was worse than evening performance. With respect to the overall dose effect, performance was worse under the 4-mg dose condition than under either the placebo or 2-mg conditions. For the three levels of ADT, only the difference between ADT2 and ADT0 was significant; performance with ADT2 was poorer than with ADT0. Results of contrasts performed on the adjusted means of the three dose conditions and the three levels of ADT are shown in Table 112.

Table 112.

Contrasts for dose and ADT main effects for scores on ZITA, task 1.

=====			
	Contrast	F	p

Dose	0 mg-2 mg		NS
	0 mg-4 mg	6.92	0.0251
	2 mg-4 mg	6.60	0.0280

ADT	A0-A2	6.46	0.0293
	A0-A1		NS
	A2-A1		NS
=====			

Percent of total

The analysis of the percentage of total number of tones to which there was a response indicated a significant main effect for dose ($F(2,21)=3.84, p=0.0379$). Contrasts revealed poorer performance under the 4-mg dose than under the 2-mg dose, but there were no differences found elsewhere.

Percent correct

The analysis of the percentage of correct responses out of the number of total responses revealed a significant session by ADT interaction ($F(1,11)=5.49, p=0.0389$). A review of the simple effects (Table 113) showed this interaction was attributable to a slight improvement with ADT1 performance in the evening session compared to the noon session ($F(1,11)=5.38, p=0.0406$). The analysis further revealed a main effect for the dose factor

$F(2,21)=4.24$, $p=0.0284$) which was a result of poorer performance under 4 mg than under 2 mg ($F(1,10)=6.36$, $p=0.0303$).

Table 113.

Adjusted means of transformed percent of correct responses for session X ADT interaction on ZITA, task 1.

Session	ADT	
	ADT2	ADT1
Noon	3.0081	2.7177
Evening	2.9150	2.8181

Tones missed

The results of the measures of association initially used to suggest which model best fit these data indicated the interaction between dose and session, and the main effects of dose, session, and ADT were all significant (Table 114). The dose by session interaction was accounted for by a dramatic increase in the number of tones missed during the 4-mg noon session when compared to both the morning and evening sessions (Figure 37). This pattern was not seen for either the 2-mg or placebo conditions. The dose and session effects also were attributable to this increase in the number of tones missed during the 4-mg noon session.

Task 2

Tracking score

For task 2, only the dose by session interaction was statistically significant ($F(1.01,11.06)=4.89$, $p=0.0489$). Examination of simple effects for this interaction revealed the differences between sessions were significant only at the 4-mg dose ($F(1,11)=4.95$, $p=0.0479$), and dose differences were significant only at the noon session ($F(2,21)=4.30$, $p=0.0272$). Further examination of the mean performance at noon and evening sessions under 4 mg showed the session effect was because of poorer performance at noon than in the evening. The dose difference during the noon session probably was due to the tendency for performance to have declined under the 4-mg dose as

Table 114.

Tests of partial and marginal association between factors affecting number of tones missed on ZITA, task 1.

Effect	Partial association ¹⁰			Marginal association		
	df	G ²	p	df (Pearson)	Chi ²	p
ADT	1	58.51	0.0000			
Session	2	14.69	0.0006			
Dose	2	7.38	0.0250			
AS	2	1.23	0.5395	2	1.75	0.4161
AD	2	0.54	0.7652	2	1.05	0.5901
SD	4	12.43	0.0144	4	12.95	0.0115
ASD	4	2.21	0.6980			

compared to the placebo dose; however, this effect only approached significance (p=0.0598).

Among the main effects, only session was significant (F(1,11)=5.03, p=0.0465). This was due to a performance decrement at noon relative to evening, probably resulting--at least partially--from the session effect under 4 mg discussed above.

Percent of total

Analysis of the percentage of total number of tones to which there was a response indicated a 3-way interaction between dose, session, and ADT (F(1.29,14.23)=7.61, p=0.0109). Also, there were significant two-way interactions between dose and session (F(2,22)=5.63, p=0.0106) and between session and ADT (F(1,11)=17.45, p=0.0015). Simple effects for the three-way interaction revealed an interaction between session and ADT at both the 2-mg dose (F(1,11)=5.30, p=0.0418) and the 4-mg dose

¹⁰The likelihood ratio Chi-square statistic, G², tests the hypothesis that the difference between the full model and the proffered model is 0; in other words, the proffered model is adequate. A probability greater than .05 suggests the hypothesis cannot be rejected.

(F(1,11)=14.25, p=0.0031). The differences among means may be seen in Table 115.

Task 1

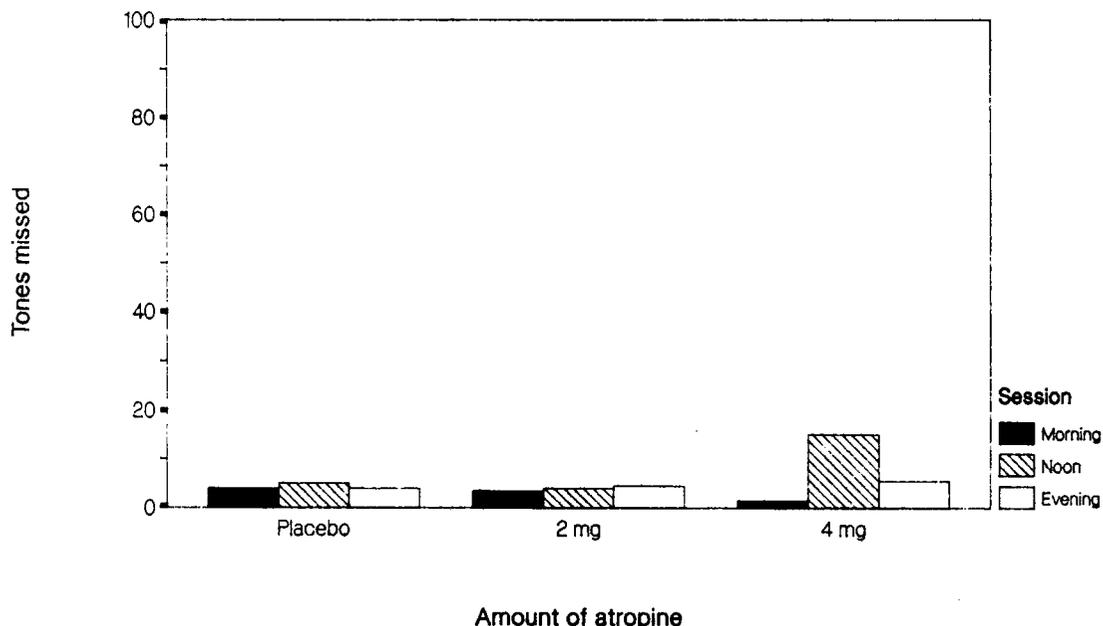


Figure 37. Dose by session interaction for number of tones missed with ZITA, task 1.

Table 115.

Adjusted means of total number of tones responded to (expressed as a percentage of those presented) for dose X session X ADT interaction on ZITA, task 2.

Dose	Session	ADT	
		ADT2	ADT1
Placebo	Noon	99.3510	97.6527
	Evening	99.0732	97.2360
2 mg	Noon	98.4031	97.0485
	Evening	98.4031	98.5762
4 mg	Noon	98.0108	92.3118
	Evening	98.2886	98.8396

The session by ADT interaction at 2 mg was attributable to a session effect only at ADT1 (the most difficult auxiliary distraction mode); however, the improvement in the evening relative to noon only approached significance ($p=0.0760$). The session by ADT interaction at the 4-mg condition was accounted for by a session effect at ADT1 ($F(1,11)=12.13$, $p=0.0051$) and an ADT effect at noon ($F(1,10)=4.93$, $p=0.0506$). Performance with ADT1 improved by 6 percent in the evening compared to noon; and, during the noon session only, performance with ADT1 was less than with ADT2. Also, the interaction between dose and ADT was significant at the noon session ($F(2,21)=3.68$, $p=0.0427$), and the interaction between dose and session was significant at ADT1 ($F(2,22)=7.51$, $p=0.0033$). These effects are attributable, in part, to a dose effect at the noon session for ADT1 ($F(2,21)=4.04$, $p=0.0327$). Contrasts for this dose effect indicated performance declined under 4 mg of atropine relative to 2 mg and placebo.

For the two-way interaction between dose and session, simple effects demonstrated a difference at noon among the dose conditions ($F(2,21)=3.52$, $p=0.0481$) resulting from a decline in performance under 4 mg relative to placebo, and an improvement under 4 mg in the evening relative to noon ($F(1,11)=8.01$, $p=0.0164$) as may be seen in Table 116. The interaction between session and ADT was, again, a result of an improvement with ADT1 in the evening relative to noon ($F(1,11)=13.67$, $p=0.0035$). The means for this effect are presented in Table 117.

Table 116.

Adjusted means of total number of tones responded to
(expressed as a percentage of those presented)
for dose X session interaction on ZITA, task 2.

Session	Dose		
	0 mg	2 mg	4 mg
Noon	98.502	97.726	95.161
Evening	98.155	98.490	98.564

Percent correct

The analysis of the percentage of correct responses out of the total number of responses revealed only a significant session

by ADT interaction ($F(1,11)=9.23$, $p=0.0113$). A review of the simple effects showed noon performance was poorer with ADT1 than with ADT2 ($F(1,10)=5.61$, $p=0.0394$); however, the difference between the two levels of ADT was not significant at the evening

Table 117.

Adjusted means of total number of tones responded to (expressed as a percentage of those presented) for session X ADT interaction on ZITA, task 2.

```

=====
Session          ADT
                ADT2    ADT1
-----
Noon             98.9216  95.6747
Evening         98.5549  98.2173
=====

```

session (the means are presented in Table 118). Simple effects also revealed a difference at ADT2 between sessions ($F(1,11)=5.41$, $p=0.0401$); noon performance was better than evening performance. There was no difference between sessions at ADT1.

Table 118.

Adjusted means of transformed percentage of correct responses for session X ADT interaction on ZITA, task 2.

```

=====
Session          ADT
                ADT2    ADT1
-----
Noon             2.9690  2.6222
Evening         2.8619  2.6599
=====

```

The only significant main effect was found for the ADT factor ($F(1,10)=5.81$, $p=0.0367$). The performance at ADT1 was poorer than at ADT2.

Tones missed

As in task 1, the measures of association used to initially construct a model of these data for task 2 indicated the dose by session interaction, and the dose, session, and ADT effects were all significant and, therefore, should be included in the initial model (Table 119). The results of the stepwise addition and deletion process confirmed the adequacy of this model ($G^2(8)=14.04$, $p=0.0808$). Here, the interaction, as seen in Figure 38, was accounted for by an increase in the number of tones missed during the 4-mg noon session and a subsequent decrease in the number missed during the 4-mg evening session (relative to the predose morning session). In addition, the more rapid rate of distraction tones (ADT1) was associated with significantly more misses than the slower rate (ADT2) regardless of dose or session.

Table 119.

Tests of partial and marginal association between factors affecting number of tones missed on ZITA, task 2.

Effect	Partial association			Marginal association		
	df	G^2	p	df (Pearson)	χ^2	p
ADT	1	244.86	0.0000			
Session	2	17.69	0.0002			
Dose	2	43.90	0.0000			
AS	2	3.78	0.1511	2	3.71	0.1565
AD	2	2.48	0.2892	2	2.41	0.2996
SD	4	11.38	0.0226	4	11.31	0.0233
ASD	4	7.85	0.0974			

Task 3

Tracking score

Analysis of the task 3 tracking scores revealed a dose by session interaction ($F(2,22)=3.52$, $p=0.0473$) because of session differences only under the 4-mg dose ($F(1,11)=5.82$, $p=0.0344$), much as in task 2 (Table 120). When this interaction was examined another way, there was a difference among the dose

compared to both the placebo and 2-mg conditions for ADT1; while there was a steady, but less dramatic, increase in the number of tones missed with increasing doses of atropine for ADT2 (Figure 39). The dose effect is indicative of the greater number of tones missed during the 4-mg condition relative to either the placebo or 2-mg conditions.

Task 3

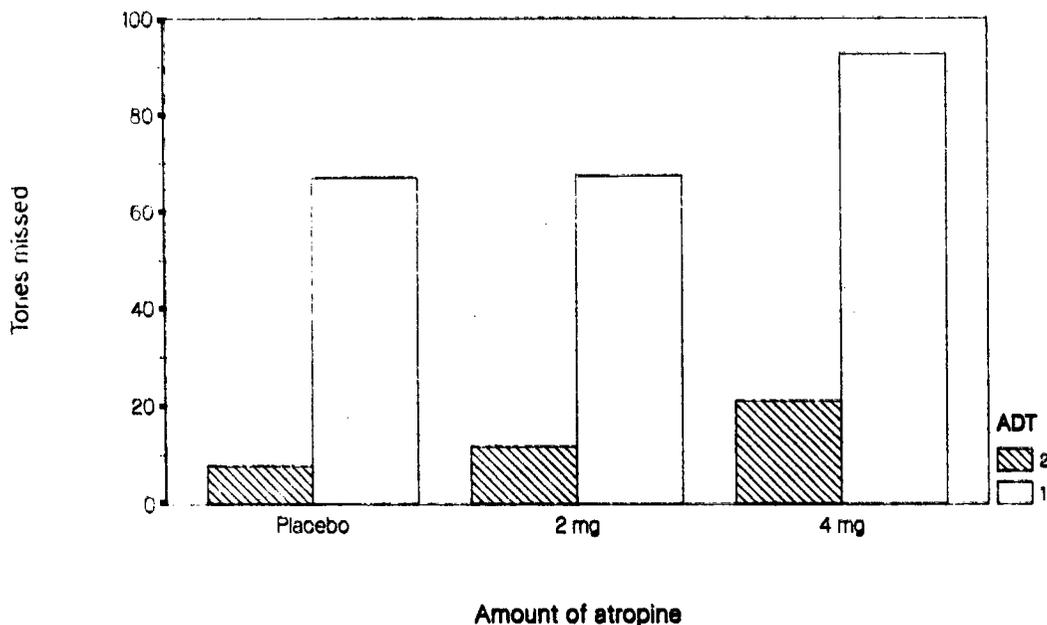


Figure 39. Dose by ADT interaction for number of tones missed with ZITA, task 3.

Discussion

General subjective observations

Although each subject was exposed to a wide array of tests designed to identify the atropine effects of interest to operational and research communities, there were many noteworthy drug-related effects identified only by observations from members of the research team. Most of these atropine effects could potentially impact on the performance of soldiers and their units, making it essential these observations be reported, even though they were not statistically evaluated. However, before noting the specific comments or complaints, some points will be noted about the composition of our sample of research participants.

Selection and screening of subjects

In the selection of subjects, there were many special criteria which had to be met before an aviator was tested. Thus, many potential participants were disqualified either prior to their arrival at the Laboratory or during the initial medical screening.

All subjects were required to take an EKG stress test to evaluate their cardiovascular system for pathology, such as coronary artery disease. Some conditions may be life threatening when aggravated by the use of atropine. One volunteer was disqualified for a positive EKG stress test and was later discovered to have mitral valve prolapse. One volunteer, although not disqualified, was discovered to have labile hypertension which previously had not been diagnosed.

All subjects were required to take an intradermal test dose of atropine to rule out any allergy or sensitivity to atropine. One volunteer was disqualified for a positive allergic/sensitive reaction to the test dose of atropine after he subsequently developed pain in the tested arm which lasted 1-2 days. Upon a second challenge, he had 10-11 cm of induration within 10 minutes at the site of the intradermal test-dose injection, and within 1-2 hours he subsequently developed pain in the tested arm which lasted about 1-2 days. He was considered to be allergic/sensitive to atropine and was disqualified from further testing. One must consider the significance of this one positive allergic reaction when considering using atropine on a large population of people. The exact amount of allergy to atropine is unknown, but allergic responses must be considered as a definite risk to the population.

Many other volunteers were disqualified due to the protocol selection requirements. Some volunteers were too old, some wore glasses, some had a refractive error greater than 1 diopter of hyperopia, etc. Therefore, all of the subjects who were actually used in this study had good vision with good accommodative power. The refractive error of all the selected subjects was less than 1 diopter of hyperopia on a cycloplegic examination; therefore, the selected subjects had little if any latent hyperopia, which can cause a loss of visual acuity as it becomes manifest with atropine.

Clearly, our standard of selection for subjects was much more stringent than the selection of aviators likely to fly combat missions in the event of any future conflict. These differences must be kept in mind when comparing the results in

this test group to another population as well as when attempting to generalize to an operational setting.

Subjective impressions

General observations concerning the effects of atropine indicated subjects appeared to tolerate the 2-mg dose fairly well. Many became jovial, told jokes, and seemed more talkative under the influence of this smaller dose. In fact, the general appearance characterized mild intoxication. None of them complained about the way they felt, although a few reported problems with dry mouth and blurred vision. Conversely, most of these subjects did not appear to tolerate the 4-mg dose of atropine well. They often became withdrawn, less talkative, short-tempered, and their general behavior frequently reflected the "surly drunk." Some complained this dose was indeed unpleasant, and they did not like the way it made them feel. In fact, those subjects who received the 4-mg dose of atropine as their first dose were very wary of receiving another dose. Since the subjects did not know how much atropine they had already received, they reasoned that if this was only the 2-mg dose, they did not want to experience the 4-mg dose.

All of the subjects complained of blurred vision and dry mouth. During the flights, several of the subjects complained of feelings of a full bladder; therefore, the aircraft was landed so they could urinate. Several of the subjects complained of feelings of fatigue and the desire to rest or sleep. A couple of subjects complained of constipation, for which they were treated. A few of the subjects complained of vertigo feelings when flying instruments with the use of the hood, and one subject vomited after landing. Several of the subjects commented they did not want to bank the aircraft or perform some of the other requested maneuvers because they felt they would become disoriented and experience vertigo. One subject had a heart rate which exceeded protocol requirements and the flight had to be terminated. One subject had an elevation of body temperature which exceeded protocol requirements and had to be cooled down with ice packs.

Although, the subjects and medical monitor were not informed of the dose order, the recognizable effects of atropine made it quickly apparent to both the medical monitor and the subject whether atropine or placebo had been given. The increase in heart rate, the dryness of the mouth, the blurring of vision from loss of accommodation, and the dilation of the pupils were quickly recognized as signs of atropinization.

Even though the subjects recognized the effects of atropine upon their physical and mental states, they appeared to lack judgment concerning these effects upon their performance. For

some, atropine appeared to impair judgment and reduce vigilance and concern down to obliviousness and apathy. Just as a "drunk" driver frequently believes he can drive with no problems, some atropinized pilots seem to believe they can fly with no problems. Some subjects appeared to be unaware of their limitations. One pilot appeared to be preoccupied with the recognition that his performance had led to a mistake, and this preoccupation eventually contributed to totally losing control of the aircraft.

Continuing on that line, the most disconcerting effect observed was the "atropine apathy" seen to occur in several subjects. This apathetic attitude combined with judgment impairments and a short temper may constitute one of the most significant atropine effects the operational community will face. Under the influence of 4 mg of atropine, some aviators may simply choose not to perform their assigned mission. Others may "go through the motions" without the proper amount of concern and precision.

Complicating the major impact of performance reductions occurring as a function of decreased motivation is the likelihood that neither the performance reductions nor the decreased motivation will be accurately sensed by the atropinized pilot, which places him in a vulnerable position. The atropinized pilot is not a sober pilot because he is suffering from the influence of a drug which mimics many of the effects of alcohol.

Flight performance

Summary of safety pilot notes

Before discussing the results of the statistical analyses of flight performance data, several observations recorded by the safety pilot during test flights are summarized below. This information is considered important to document atropine-related effects which could not be statistically examined, but which are nonetheless noteworthy.

One subject reported inability to see small objects on the map during his afternoon flight under 4 mg; but his morning flight was good, except for the ILS. One subject failed to perform 30 degree banks where required during his afternoon flight under 4 mg, but his morning flight was good also. One subject's heart rate exceeded the medical monitoring limits (150 beats per minute for more than 15 minutes), causing the flight to be terminated, on the morning of his 4-mg dose day. This subject reported feeling "light headed," and after returning to the Laboratory, he was allowed to lie down until the noon testing session. He did perform an uneventful afternoon flight. On the final dose day for this same subject, he reported feeling the

effects of the dose (2 mg) 8 minutes after injection, but there were no significant problems either in the morning or in the afternoon.

During the morning of one subject's 2-mg dose day, he made three missed approaches while attempting to enter the confined area; however, this was the subject's first dose-day flight. A similar problem did not recur on subsequent days, although his performance was degraded under 4 mg. One subject was notably nervous during both the morning and afternoon flights under 2 mg. However, this was also this subject's first dose-day flight, and similar behavior was not noted on subsequent flights even though his flight performance was not up to his ability under 4 mg. On the morning of this subject's 4-mg dose day, his core temperature was up to 38.5°C by the time of drug administration. Since remaining at this body temperature for more than 15 minutes would have required terminating the flight, the safety pilot immediately climbed to 2000 feet after take-off in order to reach cooler ambient temperatures. This strategy worked, and the flight was conducted normally.

One subject, during the morning of his 4-mg day, reached down and set the radio magnetic indicator (RMI) 60 degrees off course prior to the final "instrument" straight and level. He left the RMI set off course and the safety pilot eventually had to tell the subject the correct heading. This same subject, during the afternoon of his 4-mg day, used an excessively steep approach angle while entering the confined area and landed between two trees. He nearly hovered into the tree in front of the aircraft, and then he almost hovered into the one behind the aircraft. After he was instructed to stop, he took off from the confined area and came around for another very steep approach. He terminated at approximately 75 feet above the ground and lost control of the aircraft. The safety pilot took the controls in order to prevent a crash. Following all of this, the subject performed his entry into inadvertent IMC, his instrument straight and level, and his ILS approach. During the last straight and level, heading was off by 20 degrees. While tracking in on the localizer, the subject reset his altimeter to what he thought the safety pilot's altimeter was reading (he didn't comment, he just did it). One final comment about this particular 4-mg day was that this subject was packed in ice during the flight in order to keep his core temperature within the safety limits; so, heat stress was also a factor. On the subject's next flight (2 mg), his performance remained somewhat variable (probably partially because of anxiety), but there were no significant safety problems. However, it was again necessary to put cold packs in the subject's flight suit during the afternoon flight in order to reduce his core body temperature (which was fluctuating around 38.4°C - 38.5°C).

Another subject managed to perform an uneventful flight during the morning of his 4-mg dose day, but overshot his descending left turn by rolling out 180 degrees too late. He complained of feeling nauseated and dizzy. His afternoon flight was satisfactory except he failed to perform the full 720 degrees of his steep left turn (rolling out after only 540 degrees), and his airspeed control was noted to have been poorer than usual. During his 2-mg morning flight, this subject complained of a dry mouth and slightly blurred vision, and these problems were accompanied by a loss of some precision on the flight profile. However, in the afternoon, there were no complaints, and the flight went well.

The only noteworthy comment made about another subject's dose-day flights was that he was very irritable. Particularly during his last test day (2 mg), this subject would occasionally make abrupt flight control inputs during times when he "lost his temper" with himself.

One subject was reportedly unable to hover during confined area operations on the morning of his 4-mg dose day, but the rest of the flight (except for the ILS) went well. The next subject demonstrated somewhat erratic aircraft control on both the placebo and the 4-mg days (his first and second dose days). His 2-mg flights were his best, even though some deteriorations were seen in the morning. One other subject's 2-mg flights were good also; however, on the morning of his placebo day, he apparently "stressed himself out" trying to fly perfectly and didn't do very well. His afternoon flight was good and his 4-mg flights were okay also. Another subject failed to perform the right descending turn properly during the morning of his 4-mg day. This subject continued descending through 1000 feet (down to 650 feet), and he turned over 100 degrees past the specified roll-out point. During the afternoon flight on his 4-mg day, this same subject was noted to have performed well on three or four maneuvers and then to have performed erratically on the next one. However, it was noted also that even on this subject's placebo day (the last day in his sequence), he didn't perform as well as expected--possibly due to motivational changes.

Taken as a whole, these comments made by the safety pilot immediately after each flight highlight a few points. First, it is clear certain individuals are affected by atropine to a greater extent than are others. Thus, it may be important for aviators to experience the effects of atropine at least once during their training so they can gauge the amount of impairment they may experience in the event of subsequent drug administration. Second, there is likely an interaction between atropine effects and environment which should be considered when attempting to estimate the impact of atropine on performance. Particularly in hot weather, atropine will increase the

effects besides the dose level and the time of day. A close examination of the maneuvers involved suggests that the atropine level and the time course are probably complicated by both maneuver complexity and the sensitivity of the analyzed parameters. While all of these issues cannot be explained at this point, it seems clear that a more precise examination of atropine effects will require consideration of numerous variables.

Certainly, these findings point out the effects of atropine must be considered in terms of the type of flying required of pilots as well as the circumstances under which this flying will be done. It is important to note that, particularly under the 2-mg dose, pilots may be able to overcome many of the performance decrements that would be expected to occur as a function of either fatigue or atropine by "setting their sights" on immediate task completion and relying on sheer self-induced motivational increases to do a good job. However, it could be predicted that flight performance after atropine would degrade much more than what was seen in this study if the pilot wasn't able to look forward to an evening of rest and relaxation after the afternoon flight.

From a purely methodological standpoint, it is interesting that measures of heading and airspeed were affected by atropine administration far more often than other measures (indicating high sensitivity). Of the total 31 dose-related effects found with computer scores and safety pilot grades combined, 7 were found on heading control, 6 were found on airspeed control, and the remaining 18 were spread across 13 other measures. Thus, if limited channels of flight data are to be collected, the present findings suggest measures of heading and airspeed should comprise at least two of the total.

With regard to the two methods of flight performance measurement, it was somewhat disappointing to find there was not a one-to-one correspondence between the computer scores and the safety pilot grades. Sometimes there was substantial agreement between the two types of evaluation, whereas other times there was not. However, if the differences between computer scores and the safety pilot grades on specific measures (airspeed, altitude, etc.) are discounted and the general consistency between these data sets (the existence of a dose effect on at least some measure from each set, for instance) is emphasized, the scores and grades rarely contradicted one another. In fact, usually there was consensus regarding some sort of degradation as a function of atropine on most maneuvers. Also, there was often consensus on the general performance changes as a function of time-of-day. Thus, significant performance decrements were detectable using either type of scoring or grading system even if

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Taken as a whole, these comments made by the safety pilot immediately after each flight highlight a few points. First, it is clear certain individuals are affected by atropine to a greater extent than are others. Thus, it may be important for aviators to experience the effects of atropine at least once during their training so they can gauge the amount of impairment they may experience in the event of subsequent drug administration. Second, there is likely an interaction between atropine effects and environment which should be considered when attempting to estimate the impact of atropine on performance. Particularly in hot weather, atropine will increase the

probability of heat-stress related performance problems. Third, the irritability and short temper associated with atropine administration for some subjects may be a cause for concern. Particularly where soldiers are under the supervision of an atropinized pilot who is susceptible to such irritability, there may be problems with team efficiency and general morale.

Statistical evaluations of flight performance

Analyses of both safety pilot grades and computerized scores of flight performance showed a majority of the maneuvers flown as a part of the flight profile were degraded by injections of atropine sulfate. Some atropine-related effects were found as early as 14-20 minutes postdose. Most of the time, the larger dose of atropine was associated with significantly lower performance than what was seen under the influence of the placebo. Computer scores on four sets of maneuvers (among which were the six straight and level segments) showed atropine-related performance changes revealed as dose main effects. In every case, the significant reductions were between the placebo and 4-mg conditions, and in some cases there were reductions between the 2-mg condition and the 4-mg condition, findings which are consistent with those of Dellinger, Taylor, and Porges (1987) and Simmons et al. (1989). None of these computer-scored measures, however, revealed statistically significant reductions between placebo and 2 mg. The same general trend was also seen in the interactions of dose with either time-of-day or maneuver. While there were decrements associated with the 4-mg dose (compared to placebo and/or 2 mg), the 2-mg dose was not significantly different from placebo.

The atropine-related effects obtained with safety pilot grades were similar, but not entirely consistent with effects obtained with computer scores. Here, there were dose effects on at least one measure from every maneuver (or set of maneuvers) with the exception of the steep turns, the descending turn, and the inadvertent IMC. There were also a few interactions which involved the dose factor. In 10 cases out of the total of 17 dose-related effects, performance under either dose of atropine was worse than performance under placebo. Thus, the safety pilot grades often revealed decrements attributable to the 2-mg dose, whereas the computer scores did not. Of the remaining seven dose-related effects, slightly more than half were attributable to differences between the placebo and 4-mg doses as well as differences between the 2-mg and 4-mg doses, while there was not a significant decline from placebo to the 2-mg dose. The remaining dose effects were due to performance declines from placebo to the 4-mg dose. In general, it appears the safety pilot's grades were slightly more sensitive than the computer

scores to the decrements produced under the smaller dose of atropine.

Besides the atropine-related effects, there were differences attributable to other factors such as time of day and type of maneuver. Generally speaking, several of the earlier maneuvers revealed better performance in the morning than in the afternoon (seen mainly in computer scores), while the later maneuvers indicated better performance in the afternoon than in the morning. This general effect appeared to be fairly consistent although there were some exceptions. These time-of-day effects were probably due to a combination of drug effects, fatigue, and motivational variables, although the absence of consistent effects makes a definitive conclusion impossible.

There were several other effects attributable to a combination of time-course of drug effects, maneuver ordinal position, and maneuver complexity. For instance, an examination of computer-scored vertical speed control during the two standard-rate turns (14 and 20 minutes into each flight) showed that 1) performance on the first turn was better than performance on the second turn in the morning under 4 mg, and 2) performance on the first turn was degraded from morning to afternoon under 4 mg, whereas performance on the second turn was unaffected. Also, the safety pilot grades revealed decrements (on turn rate) as a result of atropine during only the second turn, whereas there were not any decrements in turn rate control on the first turn, regardless of time of day. Taken together, these results suggest atropine's effects did not become manifest until after 14 minutes postdose; however, a further examination of the safety pilot grades calls this suggestion into question since there were fairly straightforward atropine effects on three measures in these turns regardless of whether the turn occurred first or second and regardless of the time of day.

There were similar interpretive ambiguities which involved the steep turns. Here, there was a time-of-day effect (afternoon worse than morning) on computer-scored roll control only under the 4-mg dose, whereas there were no time-of-day differences under placebo or 2 mg. This suggests both of these turns were too near the dose time in the morning (31 and 38 minutes) to have been affected by atropine during the first flight of the day, while in the afternoon, the effects of 4 mg were noticeable. Interpreting these findings in terms of time-from-dose alone, however, presents inconsistencies with what was found with the straight and level segments (at 17, 23, 35, 42, and 49 minutes) and the straight climb (at 27 minutes postdose). All of these indicated a main effect on computer-scored heading control which suggests there were small atropine-related decrements fairly soon after the dose and prior to the times of the steep turns. Therefore, there are some other factors operative in these

effects besides the dose level and the time of day. A close examination of the maneuvers involved suggests that the atropine level and the time course are probably complicated by both maneuver complexity and the sensitivity of the analyzed parameters. While all of these issues cannot be explained at this point, it seems clear that a more precise examination of atropine effects will require consideration of numerous variables.

Certainly, these findings point out the effects of atropine must be considered in terms of the type of flying required of pilots as well as the circumstances under which this flying will be done. It is important to note that, particularly under the 2-mg dose, pilots may be able to overcome many of the performance decrements that would be expected to occur as a function of either fatigue or atropine by "setting their sights" on immediate task completion and relying on sheer self-induced motivational increases to do a good job. However, it could be predicted that flight performance after atropine would degrade much more than what was seen in this study if the pilot wasn't able to look forward to an evening of rest and relaxation after the afternoon flight.

From a purely methodological standpoint, it is interesting that measures of heading and airspeed were affected by atropine administration far more often than other measures (indicating high sensitivity). Of the total 31 dose-related effects found with computer scores and safety pilot grades combined, 7 were found on heading control, 6 were found on airspeed control, and the remaining 18 were spread across 13 other measures. Thus, if limited channels of flight data are to be collected, the present findings suggest measures of heading and airspeed should comprise at least two of the total.

With regard to the two methods of flight performance measurement, it was somewhat disappointing to find there was not a one-to-one correspondence between the computer scores and the safety pilot grades. Sometimes there was substantial agreement between the two types of evaluation, whereas other times there was not. However, if the differences between computer scores and the safety pilot grades on specific measures (airspeed, altitude, etc.) are discounted and the general consistency between these data sets (the existence of a dose effect on at least some measure from each set, for instance) is emphasized, the scores and grades rarely contradicted one another. In fact, usually there was consensus regarding some sort of degradation as a function of atropine on most maneuvers. Also, there was often consensus on the general performance changes as a function of time-of-day. Thus, significant performance decrements were detectable using either type of scoring or grading system even if

the two systems did not entirely agree on the specific parameter suffering the most degradation.

Reasons for the discrepancies between computer scores and safety pilot grades are unclear. Most of the maneuvers had a very precise point at which scoring began and ended; thus, it is unlikely the computer was scoring performance on a different segment of a given maneuver than the safety pilot. However, it is possible the safety pilot was influenced to some extent by knowledge of how long it took subjects to prepare for each maneuver (and how accurately they prepared) once they were told to do so. The computer, of course, did not begin scoring until the maneuver was started (as specified by the safety pilot). Therefore, significant degradations may have been seen in the amount of time or the accuracy with which each maneuver was prepared, and this could have been considered in the safety pilot grades, whereas the computer scoring would have missed these initial problems. Also, the safety pilot may have been influenced by subtle behavioral changes on the subject's part. Regardless of the differences between the two grading systems, however, there was generally good agreement between safety pilot assessments and computer assessments of flight performance.

The sensitivity of particular maneuvers is not quite so straightforward. First, removing a single maneuver from the constellation of all maneuvers included in this profile could very well change any subsequent performance on other maneuvers. Secondly, even if one could reliably remove a given maneuver without worrying about the interdependency among it and the others included, our results would not help much in this selection process. The findings of the present research indicate there was no single maneuver or pair of maneuvers especially sensitive to atropine effects in comparison with the others. In fact, just tallying up the number of dose-related effects, irrespective of the measure involved, revealed a fairly even distribution among the various flight maneuvers used. The only two maneuvers which showed no atropine-related effects were the standard-rate descending right turn and the inadvertent IMC. Next to these, the two steep turns were only slightly more sensitive. Thus, if a limited number of maneuvers must be used, these should probably be omitted.

In summary, the results of the present investigation are of utility to the operational community as well as to the research community. In an operational vein, aviators who mistakenly administer 4 mg of atropine sulfate in the absence of nerve agent likely will experience decrements in flight performance which will consist of reduced accuracy in maintaining precise headings, problems in exercising precise airspeed control, and various difficulties with control of other parameters such as altitude, vertical speed, roll, slip, and pitch. Judgment will be impaired

in some aviators. The 2-mg dose of atropine also likely will be associated with decrements in flight performance, although these will be fewer in number and smaller in magnitude than the effects found with the 4-mg dose.

At higher altitudes it is improbable any of these decrements will seriously jeopardize the safety of aircraft and crew so long as the aircraft functions normally, the weather is good, the mission does not involve tight formation flight, and no emergencies or other unexpected, problematic events occur. However, at lower altitudes, particularly in confined areas, it is certainly possible 4 mg of atropine will impair the safety of aircraft and crew, and mission success will be questionable. One subject lost control of the aircraft while attempting to land in a confined area, and one subject was unable to hover well enough to satisfactorily perform an out-of-ground-effect hover maneuver. Commanders and individual aviators should be aware that atropine's effects on flight performance generally become manifest fairly quickly (as early as about 14 minutes postdose as indicated by safety pilot grades, and 20-30 minutes postdose as indicated by computer scores). Some of these effects lasted for at least 7.5 hours postdose.

Members of the operational community should bear in mind these results should be interpreted cautiously. The findings reported here were obtained with subjects who were well-rested, well-fed, and generally well-cared-for. Also, these subjects were not required to perform many of the more mundane, but very important, aviator tasks such as preflighting the aircraft, managing personnel, communicating on the radio, planning flight paths, and ensuring the safety of the crew. The safety pilot always took care of these details. Therefore, any effects noted in this study could be expected to become even more pronounced in the more stressful conditions encountered in actual operational flying.

Also, the issue of training, briefly mentioned in the method section, should be carefully considered by those in the operational community as well as those conducting flight research. From the operational point of view, some atropine effects could have been more severe had the aviators not been thoroughly pretrained on the flight tasks. From a research point of view, the training was beneficial in that it eliminated a myriad of statistical problems which would have resulted from practice effects contaminating experimental results.

Finally, from a research perspective, the safety pilot was paramount in obtaining data of sufficient quality to survive the confounds of individual differences, weather, and air turbulence. The safety pilot -- who makes every single flight, who carefully briefs each subject, who ensures maneuvers are precisely

delimited within the actual starting and ending points, and who maintains tight control over the aircraft environment -- will ultimately guarantee the data is accurate and usable.

Vision battery

The effects of atropine on the visual system have been well established in the literature. Not surprisingly, the results of our investigation confirm these earlier findings. Pupil diameter increased and accommodative ability decreased with increasing doses of atropine. Atropine also produced increases in the likelihood a subject would exhibit esophoria and left hyperphoria in near vision, both of which would tend to cause problems with double vision. Atropine caused an increased accommodative effort which, synergistically, increased the convergence response resulting in esophoria due to over-correction. Furthermore, atropine produced a reduction of contrast sensitivity for both near and distant vision. Also, there was a loss of stereoscopic vision which suggests problems with accurate depth perception.

These findings have serious implications for operational flight. One subject reported flying with one eye closed during his 4-mg afternoon flight in an effort to eliminate the double vision he was experiencing, and 3 of the 12 subjects reported loss of fusion and double vision after administration of 4 mg of atropine. Two of the 12 subjects reported having difficulty adjusting focus from outside the cockpit to inside. The average point of accommodation for the group 20 minutes after completion of the 4-mg morning flight was 26.7 cm for the right eye and 25.0 cm for the left eye. However, two subjects exceeded the Prince rule maximum value of 50 cm. Therefore, the maximum value of 50 cm was entered into the data set for these subjects' 4-mg noon and evening sessions. Since the pilots' eyes are approximately 66 cm from the instrument panel, it is quite possible a certain portion of the aviator population would be unable to focus on their instruments under the influence of 4 mg of atropine. Problems with map reading would be even more likely, and the loss of contrast sensitivity may seriously compromise an aviator's ability to acquire visual targets, recognize navigational landmarks, and avoid hazardous objects in flight.

Electroencephalographic activity

The effects of atropine on EEG activity were examined to assess the global effects of the drug on central nervous system activation. Past literature suggests atropine at certain dosages is associated with central nervous system effects, such as slower EEG activity (reflecting reduced overall activation), as well as cognitive effects (Longo, 1966). The slower EEG activity and

reductions in the percentage of alpha have been found to be maximal at about 3 to 4 hours postdose (with 10 mg orally), but they persist for up to 7 to 10 hours (Ostfeld, Machne, and Unna, 1960). Again, both of these effects and their time course suggest generalized and persistent sedation which may contribute to degraded performance. Our findings support these earlier reports.

While there were some interactive effects between dose, time of day, and eyes-open/eyes-closed, the number of these was not as prevalent as would have been predicted. The dose effects seemed to be spread fairly evenly among the different levels of each factor, but the most frequently affected EEG activity was in the alpha band where the amount of the activity was significantly reduced by 4 mg of atropine. As for the impact of time of day, the dose effects appeared to have been larger at the first postdose (noon) session than at the second. However, this was statistically significant only at O_2 where there were noon session elevations in theta with increasing atropine and noon session reductions in beta (4 mg versus placebo), whereas the same effects were not seen in the evening. Everywhere else, the effects of atropine generally remained from noon to evening. The effect of opening and closing the eyes was somewhat unusual in that there were reductions in the percentage of both delta and beta activity at F_2 , C_2 , and P_2 from eyes-open to eyes-closed. There was, however, no concurrent significant increase in alpha. Perhaps this finding can be explained on the basis of large variability among subjects, tendencies toward more complex interactions, alpha blockade during eyes-closed due to anxiety, or alpha elevations during eyes-open due to fatigue. Also, it is likely the analysis of relative power rather than absolute power and the use of analysis of covariance rather than analysis of variance may have complicated interpretations.

The straightforward time of day (session) effect was reasonably consistent across the midline electrodes. Specifically, there were higher levels of theta activity at F_2 and C_2 during the noon session (about 3 hours postdose) than during the evening session (about 8 hours postdose). There was a concurrent alpha elevation at F_2 , P_2 , and O_2 from noon to evening. Also, there was an increase in the ratio of fast to slow activity and an increase in the mean frequency of EEG from noon to evening which was seen only at F_2 . These results were probably due to lower apprehension with lessening effects of atropine 8 hours postdose as opposed to 3 hours postdose.

Finally, the large number of dose effects seen across all of the midline leads clearly lend support to earlier findings concerning the overall effects of atropine. The generalized slowing of EEG activity (reflecting reduced activation) was depicted by increases in delta at F_2 , C_2 , and P_2 ; increases in

theta at P_z and O_z; reductions in alpha at F_z, C_z, P_z, and O_z; decrements in the ratio of fast to slow activity at all four midline leads; and decreases in mean frequency at both P_z and O_z. In every case, the 4-mg dose was involved in the observed effects. Most of the time there were differences between the 4-mg dose and the placebo dose, but about 50 percent of the time there also were differences between the 4-mg dose and the 2-mg dose. In only one case was there a significant change between 2 mg and placebo. Thus, the limited impact of the smaller amount of atropine seen with other measures collected during this investigation also were observed with EEG activation. Also, the pronounced effect of the larger 4-mg dose is quite consistent with the disruptive effects of this dosage level seen on flight performance, tracking, and cognition. These EEG results suggest generalized atropine-related central nervous system sedation, which may account for several of the observed performance changes.

Event related potentials

The effects of atropine on ERPs were of interest because of what they suggest in terms of both stimulus identification and information processing. As for the stimulus identification effects, atropine is known to increase pupil size and induce at least some degree of visual blur. As for the cognitive processing effects, it was expected that atropine-induced central nervous system sedation (seen with the EEG data) would be reflected in the ERP data as well. All of these factors appear to have influenced this set of electrophysiological data.

The N75 reductions evidenced by a dose main effect suggested fairly persistent atropine effects throughout the day, although visual inspection showed the most noticeable effect tended to occur at noon. However, the subsequent findings of P100 increases which occurred only in the evening with the first five check patterns, tended to cloud interpretations. Although some of the differences between results on these early components may have been partially due to the chosen scoring procedure, other explanations are likely more accurate.

It is plausible that the observed reductions in N75 amplitude, particularly at noon, were caused by both the sedative effects of atropine (seen in the EEG data) and the generalized vision disturbances discussed earlier. Both types of effects were found to be persistent, and both would tend to influence this early component of the evoked response. In fact, the normal changes in N75 amplitudes which would have been expected in response to different stimuli were found to be suppressed by both the 2-mg and the 4-mg dose. The fact that P100 amplitudes revealed differential sensitivity to atropine depending on

whether the test was given at noon or in the evening probably resulted from a combination of factors. Since atropine increased the amount of pupil dilation experienced by subjects, this would have made the perceived brightness of the check patterns more intense. Such a perceived change in the stimulus would have contributed to larger amplitudes for the P100 component. However, initially this effect was suppressed by the generalized atropine-related sedation at the first postdose session, whereas later in the day, the anticipated P100 elevation was seen to have occurred.

One other effect found with the early-component evoked responses to this array of check patterns, was the generalized session effect. From the noon session to the evening session, there was an overall increase in both N75 amplitude and P100 amplitude which may have reflected increases in attentiveness to incoming stimuli (Brandeis and Lehmann, 1986) as the day progressed. It is conceivable subjects found it easier to concentrate on the visual stimuli at the conclusion of the testing day than at the middle of the testing day because any atropine effects would have largely subsided by evening and the most stressful testing of the day already was complete.

Finally, the findings with regard to the P300 data were interesting. To start with, the P300 component is thought to be a portion of the evoked response virtually independent of the stimulus parameters (Brandeis and Lehmann, 1986). In fact, Sokol (1986) found blurring of the stimulus pattern used to evoke this cortical response did not suppress the P300 component, even though the P100 amplitude was attenuated. While P300 latencies have been found to increase when the relevant stimuli are markedly obscured to the point where subjects have trouble discerning the eliciting event (Fagan, Westgate, and Yolton, 1986), this level of impairment was not present here (where the eliciting stimulus was a complete reversal of a large 4x8 checkerboard pattern). Thus, it was felt the P300 provided at least some index of cognitive processing when considered along with the behavioral data.

Results of the analysis of both amplitude and latency data on this component indicated atropine administration significantly lengthened the latency and reduced the amplitude of the P300. Since P300 latency has been demonstrated to be an indicator of the amount of time required for stimulus evaluation (McCarthy and Donchin, 1981; Magliero et al., 1984), these data suggest atropine decreased the speed of cognition and possibly reduced the level of certainty in making decisions (or in paying attention to the task at hand). These effects agree with what was found from the resting EEG data, and they provide further insight into the atropine-induced changes which contributed to various performance decrements.

Performance assessment battery

The data from the performance assessment battery indicate atropine has detrimental effects on both cognitive and psychomotor aspects of performance. Performance was degraded on measures of visual search, reasoning, quantitative, short-term memory, and psychomotor abilities. In most cases, atropine exhibited its influence on speed-related measures (mean RT for correct responses, speed, and throughput). These influences were typically characterized by increases in RT and decreases in the speed of responding, effects which are consistent with the general sedative effects of atropine discussed earlier. In general, 4 mg of atropine accounted for the decrement in performance while the difference between placebo and 2 mg was usually not significant.

Curiously, in six-letter search and logical reasoning, there was an apparent facilitation of performance for speed-related measures under the 2-mg dose, but the differences between placebo and 2 mg were not significant in either case. A similar facilitation effect was observed by Seppala and Visakorpi (1983) on a measure of RT with a 0.85-mg oral dose of atropine compared to both placebo and a 1.70-mg oral dose.

In cases where degradation of performance occurred, the greatest decrements were seen during the noon session (approximately 3.5 hours postdose). Performance typically recovered by the evening session (approximately 9 hours postdose). When there was an interaction between dose and session, differences between sessions were not significant in the placebo condition, but they were in the 2-mg and 4-mg conditions. This finding argues against the interpretation of the improvement as a result of circadian fluctuations in performance.

Because of atropine's well-documented effects on vision, it is necessary to consider whether it had its effects on cognitive performance through the central nervous system or through its degrading influence on the visual system. If the pilots tested in the present investigation had difficulty seeing the stimuli presented, conclusions would be difficult to draw from the findings. In an attempt to control for this confound, subjects were provided with spectacles designed to correct for various degrees of hyperopia. However, only a few subjects chose to use them. Since the subjects' viewing distance from the screen was not precisely controlled, it was possible for them to adjust their viewing position to compensate for a moderate loss of accommodation. Furthermore, the fact that improvements as well as decrements in performance were observed argues against a peripheral visual deficit as the sole explanation of the

cognitive performance findings. Instead, atropine-induced central nervous system effects, as depicted in the EEG and P300 data, were probably of paramount importance, particularly regarding response speed.

The speed of responding was typically reduced during both sessions (3.5 hours and 9 hours postdose) under the influence of atropine. In some cases, the slowdowns may have been deliberate on the part of subjects as they attempted to preserve the accuracy of their performance. Since these cognitive tasks were subject-paced, they were conducive to such a sacrifice of speed in a speed-accuracy tradeoff (Rabbitt and Vyas, 1970; Wagenaar and Stakenburg, 1975). This strategy apparently met with some degree of success on two of the tasks, at least during the session which took place 9 hours postinjection. As could be seen from the logical reasoning and four-choice serial RT tasks, accuracy under 4 mg at the last session of the day was not degraded in comparison to placebo, whereas decrements were seen earlier.

Conversely, on one other task, the speed-accuracy tradeoff was not successful since both performance measures revealed decrements under atropine throughout both postdose sessions. On the digit recall task, 4 mg of atropine caused reductions in throughput and percent correct which persisted for up to 9 hours -- indicating there will be decrements in performance on some tasks regardless of any strategy which may be employed on the part of the individual.

Zero input tracking analyzer

A preliminary visual examination of the means of the ZITA data showed, overall, there tended to be a consistent "disturbance" occurring about 4 hours after injection under the 4-mg atropine dose condition not present in either the 2-mg or placebo conditions. This disturbance appeared to greatly diminish or completely vanish after about 9.5 hours postinjection. The noted decrements seemed to be influenced by various combinations of dose, time, and/or task requirements.

In the relatively simple velocity-tracking task, the score depended on the time since injection and a combination of auxiliary distraction task (ADT) and atropine dose. The response findings (with response percentages, percent correct, and missed tones) depended on the dose and, in the case of the percentage of correct responses, a combination of ADT difficulty and the session. The number of tones missed depended on ADT difficulty and, to some degree, a combination of the session and the dose. Degraded performance generally was associated with the more demanding ADT, the higher dose of atropine, and/or the shorter

elapsed time from injection. Our findings suggest trackers' reserve capacities may have allowed them to handle the distraction of the secondary task at the lower dose of atropine, but not at the higher dose.

Significantly reduced tracking performance was associated with the 4-mg dose in comparison to either or both the placebo and 2-mg doses within the same ADT mode, but tracking was never impaired under the 2-mg dose. In other words, ADT difficulty was not a significant factor until 4 mg of atropine was administered. It was also noted under the 4-mg dose, subjects responded to fewer elements of the secondary task (ADT tones) than they did under the lower doses, and they incorrectly identified more of the tones to which they did respond. These findings suggest activities involving machine-paced tasks with a secondary mental/cognitive element will be degraded when atropine is in use. Operational performance on jobs where there are secondary requirements to correctly locate, identify, and respond to targets within short time periods may, therefore, be compromised shortly after atropine injection. However, performance will likely recover substantially by about 9 hours postinjection.

In the more difficult acceleration-tracking task, the tracking score was affected by a combination of the session and dose factors where the level of auxiliary distraction was not important. The findings with regard to the other performance measures, however, depended on a more complex combination involving the difficulty of the secondary task, the time from dose, and the amount of atropine.

Once again we found decrements in tracking performance associated with the 4-mg dose a relatively short time after injection. Performance was not seriously disturbed by 2 mg. Also, it had returned to near-normal by 9.5 hours postinjection under the 4-mg dose condition. Here, the added complexity of ADT did not seem to affect the tracking score, but it did affect performance on the secondary task itself.

In the most difficult tracking task, the pattern changed again. Here, the tracking score depended on the combination of session and dose as was the case with task 2; but, this time, ADT difficulty was important as well. The number of tones missed was affected by the session and by a combination of ADT difficulty and dose.

Once more, the effect of the 4-mg dose appeared about 4 hours after injection (the first postdose test time); and again it was associated with the more complex task. ADT difficulty exerted the greatest influence by far in task 3. Both the tracking errors and the number of missed tones jumped dramatically as the secondary task demands increased. Thus,

these indications of poor performance suggest subjects' reserve capacities could not absorb the additional distraction without substantial performance losses on this, the most difficult task.

Overall, the degradation observed under the higher dose condition, but not under the lower one, gave further credence to the findings of Penetar and Beatrice (1986) and Simmons et al. (1989) that 4 mg of atropine causes a disturbance in tracking, while 2 mg does not. These data show that accuracy on machine-paced tasks, as opposed to subject-paced tasks like PAB, are more susceptible to atropine-induced decrements. These data also indicate psychomotor tasks involving cognitive elements combined with distractions may be more susceptible to the effects of atropine than those of a purely psychomotor nature, as would be expected because of increased cognitive demands. Finally, they demonstrate the effects of atropine, at least as they pertain to operating the ZITA, wear off within about 9 hours.

Recommendations

1. Because of the significant global effects of 4 mg atropine, aviators should avoid flying under the influence of atropine whenever possible. Atropine is **not** a pretreatment drug.
2. After a 4-mg dose of unchallenged atropine, performance decrements should be expected within 30 minutes postdose. Aviators should return to base and wait at least 12 hours for the drug effects to dissipate. Even then, they should obtain a clearance from their flight surgeon before returning to duty.
3. Helicopter operations which require very precise aircraft control and quick decisions (confined area operations, formation flights, etc.) should be especially avoided after atropine administration.
4. Although 2 mg of atropine is less a cause for concern than 4 mg, flight under the influence of this smaller dose should not be attempted (except to return to base) since the chances of flight-related safety problems will be increased.
5. Pilots should expect the added stress of an actual operational scenario to compound the atropine-related performance problems observed in this investigation. Heat stress, particularly, is cause for concern.
6. Future research should be conducted to examine the effects of atropine administered in combination with pralidoxime chloride.

7. Future research should be conducted to investigate the effects of atropine and pralidoxime chloride administered after pretreatment with pyridostigmine.
8. Future research should examine the effects of atropine alone or in combination with the substances listed above in other aircraft to include UH-60 and AH-64.
9. Future atropine research should include a 6-mg dose condition since 6 mg are available in the soldier's first aid kit for self-administration.

References

- Anderson, S., McGuire, R., and McKeown, D. 1985. Comparison of the cognitive effects of premedication with hyoscine and atropine. British journal of anaesthesia. 57: 169-173.
- Baker, R., Adams, A., Jampolsky, A., Brown, B., Haegerstrom-Portnoy, G., and Jones, R. 1983. Effects of atropine on visual performance. Military medicine. 148: 530-535.
- Banderet, L. E., and Jobe, J. B. 1984. Effects of atropine upon cognitive performance and subjective variables. Natick, MA: U. S. Army Research Institute of Environmental Medicine. USARIEM report no. T5/85.
- Banderet, L. E., Shukitt, B. L., Crohn, E. A., Burse, R. L., Roberts, D. E., and Cymerman, A. 1986. Effects of various environmental stressors on cognitive performance. Proceedings of the 28th annual meeting of the Military Testing Association. Mystic, CT: U. S. Coast Guard Academy. 592-597.
- Bartlett, M. S. 1941. The statistical significance of canonical correlations. Biometrika. 32: 29-38.
- Brandeis, D., and Lehmann, D. 1986. Event-related potentials of the brain and cognitive processes: Approaches and applications. Neuropsychologia. 24: 151-168.
- Cadarette, B. S., Levine, L., Rock, P. B., Stephenson, L. A., and Kolka, M. A. 1986. Effects of atropine on thermoregulatory responses to exercise in different environments. Aviation, space, and environmental medicine. 11: 1051-1055.
- Cullumbine, H., McKee, W. H. E., and Creasey, N. H. 1955. The effects of atropine sulphate upon healthy male subjects. Quarterly journal of experimental physiology. 40: 309-319.
- Cullumbine, H., and Miles, S. 1953. The effect of atropine sulphate on men exposed to warm environments. Porton Down, Salisbury, Wiltshire, England: Chemical Defence Experimental Establishment. Porton technical paper no. 355.
- Dorland's Illustrated Medical Dictionary. 26th edition. 1981. Philadelphia: W. B. Saunders Company.
- Dellinger, J. A., Taylor, H. L., and Porges, S. W. 1987. Atropine sulfate effects on aviator performance and on respiratory-heart period interactions. Aviation, space, and environmental medicine. 58: 333-338.

- Department of the Army. 1984. Aircrew training manual, utility helicopter, UH-1. Washington, DC. U. S. Army training circular, TC 1-211.
- Department of the Army. 1986. Temporary flying restrictions due to exogenous factors. Washington, D.C. U. S. Army Regulation 40-8, para 4a(1).
- Dixon, W. J., Brown, M. B., Engleman, L., Frane, J. W., Hill, M. A., Jennrich, R. I., and Toporek, J. D. (eds.). 1983. BMDP Statistical Software. Berkeley: University of California Press.
- Fagan, J., Westgate, T., and Yolton, R. 1986. Effects of video display character size, clarity, and color on P-300 latency. American journal of optometry and physiological optics. 63: 41-51.
- Grieve, A. P. 1984. Tests of sphericity of normal distributions and the analysis of repeated measures designs. Psychometrika. 49: 257-267.
- Haegerstrom-Portnoy, O. D., Jones, R., Adams, A. J., and Jampolsky, A. 1987. Effects of atropine and 2-pam chloride on vision and performance in humans. Aviation, space, and environmental medicine. 58: 47-53.
- Haig, A. M., Jr. 1982. Chemical warfare in Southeast Asia and Afghanistan. Washington, DC: United States Department of State special report no. 98.
- Headley, D. B. 1982. Effects of atropine sulfate and pralidoxime chloride on visual, physiological, performance, subjective, and cognitive variables in man: A review. Military medicine. 147: 122-132.
- Himwich, H. E. 1954. Effect of large doses of atropine sulfate on EEG and personality structure. U. S. Army Chemical Center contract no. DA-108-CML-5359. Medical Laboratories contract report no. 49.
- Holland, P., Kemp, K. H., and Wetherell, A. 1978. Some effects of 2 mg i.m. atropine and 5 mg i.m. diazepam, separately and combined, on human performance. British journal of clinical pharmacology. 5: 367-368.
- Jampolsky, A., Haegerstrom-Portnoy, G., Jones, R., and Adams, A. J. 1984. Effects of atropine and 2-pam chloride on vision and performance. San Francisco, CA: The Medical Research

Institute of San Francisco. U. S. Army Medical Research and Development Command contract no. DAMD17-83-0-3198.

- Kalser, S. C., and McLain, P. L. 1970. Atropine metabolism in man. Clinical pharmacology and therapeutics. 11: 214-227.
- Kay, C. D., and Morrison, J. D. 1987. The effects of a single intramuscular injection of atropine sulphate on visual performance in man. Human toxicology. 6: 165-172.
- Kroesen, F. J. 1989. Chemical warfare--a real and growing threat. Arlington, VA: Association of the United States Army (AUSA) Institute of Land Warfare. Special report.
- Lebensohn, J. E. 1936. Scientific and practical considerations involved in the near-vision test with presentation of a practical and informative near-vision chart. American journal of ophthalmology. 19: 110-117.
- Lobb, M. L., Phillips, J. D., and Winter, A. S. 1985. Effects of atropine sulfate on aircrew performance. Arlington, TX: Department of Psychology, University of Texas at Arlington. Technical report no. 85-48.
- Longo, V. G. 1966. Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacological reviews. 18: 965.
- Magliero, A., Bashore, T. R., Coles, M. G. H., and Donchin, E. 1984. On the dependence of P300 latency on stimulus evaluation processes. Psychophysiology. 21: 171-186.
- Marzulli, F. N., and Cope, O. P. 1950. Subjective and objective study of healthy males injected intramuscularly with 1, 2, and 3 mg atropine sulfate. U. S. Army Chemical Center, MD: Chemical Corps Medical Division. Medical Division research report no. 24.
- McCarthy, G., and Donchin, E. 1981. A metric for thought: A comparison of P300 latency and reaction time. Science. 211: 77-80.
- Miles, S. 1955. Some effects of injection of atropine sulphate in healthy young men. Porton Down, Salisbury, Wiltshire, England: Chemical Defence Experimental Establishment. Porton technical paper no. 514.
- Mitchell, A., Lewis, A., Jones, H., Higdon, A., and Baer, D. 1988. Aircraft in-flight monitoring system (AIMS). Fort Rucker, AL: U. S. Army Aeromedical Research Laboratory. USAARL letter report no. LR 88-12-5-2.

- 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.
- Newhouse, P. 1987. Neuropsychiatric aspects of chemical warfare. In Belenky, G., ed. Contemporary studies in combat psychiatry. Westport, CT: Greenwood Press, Inc.
- Norman K. Walker Associates, Inc. n.d. ZITA/ADT Mk Xc: Description of equipment and tasks, checkout, programming, protocol, bibliography and operator's manual. Gaithersburg, MD.
- Ostfeld, A. M. Machne, X., and Unna K. R. 1960. The effects of atropine on the electroencephalogram and behavior in man. Journal of pharmacology and experimental therapeutics. 128: 265.
- Penetar, D. M., and Beatrice, E. S. 1986. Effects of atropine on human pursuit tracking performance. Aviation, space, and environmental medicine. 57: 654-658.
- Rabbitt, P. M. A., and Vyas, S. M. 1970. An elementary preliminary taxonomy for some errors in laboratory choice RT tasks. Acta psychologica. 33: Sanders, A. F. (ed). Attention and performance, III. 56-76.
- Robinson, S. 1953. The physiological effects of atropine and potential atropine substitutes. Department of Physiology, Indiana University.
- Rubin, L. S. 1956. The effect of atropine on the dark adaptation threshold. U. S. Army Chemical Center, MD: Chemical Warfare Laboratory. Chemical Warfare Laboratories report no. 2019.
- Sawka, M. N., Levine, L., Kolka, M. A., Appleton, B. S., Joyce, B. E., and Pandolf, K. B. 1984. Effect of atropine on the exercise-heat performance of man. Fundamental and applied toxicology. 4: 190-194.
- Scicchitano, J. P. 1990. Elite force has been trained for chemical war. Army Times. (27 August 1990): 61.
- Seppala, T., and Visakorpi, R. 1983. Effect of atropine on shooting: A field trial. Military medicine. 148: 673-675.
- Simmons, R. R., Caldwell, J. A., Stephens, R. L., Stone, L. W., Carter, D. J., Behar, I., Mitchell, G. W., Knox, F. S., Jones, H. D., and Taylor P. L. 1989. Effects of the

chemical defense antidote atropine sulfate on helicopter pilot performance: A simulator study. Fort Rucker, AL: U. S. Army Aeromedical Research Laboratory. USAARL report no. 89-17.

Sokol, S. 1986. Visual evoked potentials. In Aminoff, M. J. (ed.) Electrodiagnosis in clinical neurology. New York: Churchill Livingstone. 441-466.

Taylor, H. L., Dellinger, J. A., Richardson, B. C., Weller, M. H., Porges, S. W., Wickens, C. D., Legrand, J. E., and Davis, J. M. 1985. The effects of atropine sulfate on aviator performance. Savoy, IL: Aviation Research Laboratory, University of Illinois. ARL-TR-85-1. For U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD. DTIC no. AD-A179 078. (as USAARL report no. CR-89-9. Fort Rucker, AL.)

Thorne, D. R., Genser, S. G., Sing, H. C., and Hegge, F. W. 1985. The Walter Reed performance assessment battery. Neurobehavioral toxicology and teratology. 7: 415-418.

Vojvodic, V., Rosic, N., and Vojvodic, M. 1967. Effects of atropine sulfate on the body and some elements of fighting capability of healthy volunteers. Vojnosanit Pregled, 24(10), 522-526. (This is a restricted access document because it contains proprietary information.)

Wagenaar, W. A., and Stakenburg, H. 1975. Paced and self-paced continuous reaction time. Quarterly journal of experimental psychology. 27: 559-563.

Wetherell, A. 1980. Some effects of atropine on short-term memory (Letters to the Editors). British journal of clinical pharmacology. 10: 627-628.

Winer, B. J. 1971. Statistical principals in experimental design, 2nd ed. New York: McGraw-Hill.

Appendix A
Informed consent

U.S. ARMY AEROMEDICAL RESEARCH LABORATORY
FT. RUCKER, ALABAMA 36362

VOLUNTEER AGREEMENT EXPLANATION
FOR STUDY ENTITLED

Aviator Performance Effects of Chemical Warfare Antidotes (Atropine)

By John A. Caldwell
Principal Investigator

PURPOSE

You are being asked to participate in a research program that will assess the effects of Chemical Warfare (CW) antidotes and/or pretreatment drugs (APD) on the performance of aviators during flight missions. You will remain at USAARL facilities, building 6901, and refrain from outside contacts except in emergencies for up to a fourteen day period; you can voluntarily withdraw from the study without prejudice, but you will be required to remain until you have undergone a medical examination to assure your health and well-being.

PROCEDURES

Prior to your participation in the study, you will be given a physical examination by a flight surgeon and will be asked to fill out a medical history questionnaire.

You will be asked to fly a rotary wing aircraft performing maneuvers similar to the following: (1) basic instrument flight, (2) nap-of-the-earth (NOE) navigation (subject as copilot), (3) instrument landing system (ILS) approach, (4) tactical confined area approach, and (5) low level navigation. As an experimental subject you will be asked to fly approximately 3 hours of flight per day while wearing standard flight clothing. You will be connected via three chest electrodes, several EEG head electrodes, and a flexible rectal thermometer to physiological monitoring equipment which will monitor heart rate, body temperature, and brain activity. Quick disconnect connectors will assure rapid ingress/egress from the aircraft should it be necessary. Additionally, your psychomotor coordination, visual performance and cognitive functioning will be tested intermittently during the course of the experiment. These tests include a mood scale, feeling/tone, memory and search task (MAST), logical reasoning, matrix, two-digit addition, reaction time, digit recall and zero input tracking analyzer. Investigation personnel can explain these tests to you. Periodic urine samples will be taken to assess health and response to stress.

Once on each of the three test days you will be administered an injection containing either placebo (saline, a simulated drug) or

atropine (2 or 4 mg). The dosage strengths of the atropine will be randomly varied and you will not be told what strength is being injected. The doses of atropine, which is widely used in medicine to dilate pupils or decrease secretions, will result in increased heart rate, dryness of the mouth and/or blurred vision. The doses have been selected to be effective but safe and are, in fact, similar to the dose in the autoinjector carried by troops in the field. The object is to assess the affects of such doses on your ability to perform the functions of an aviator.

The aircraft safety pilot will be in standard US flight clothing. A medical observer and a flight surgeon will be on board during all flights as members of the research team. The flight surgeon will be on board the aircraft during the in-flight phase to provide rapid advice to the medical observer and flight crew. Complete resuscitation equipment and an emergency medical team will be available at the Laboratory.

RISKS

The medical risks associated with this project are those associated with normal flight, taking atropine and that of heat-related injuries; i.e., heat exhaustion, heatstroke, and heat pyrexia. The heat injuries will only be a problem if this protocol is exercised during warm to hot weather. This is due to the fact that atropine interferes with sweat production. An explanation of these injuries follows:

Heat Exhaustion

This disorder can be broken down into two areas: a water-deficient heat exhaustion or dehydration and salt-deficient heat exhaustion.

Water-Deficient Heat Exhaustion

It is an effect of excessive exposure to heat and becoming water-depleted due to inadequate replacement of water losses caused by prolonged sweating. Signs and symptoms: thirst, fatigue, giddiness and, in advanced stages, delirium and death.

Salt-Deficient Heat Exhaustion

It is an effect of excessive exposure to heat in which salt depletion occurs due to inadequate replacement of salt lost through prolonged sweating. Signs and symptoms: fatigue, nausea, vomiting, giddiness, muscle cramps, and in late stages, circulatory failure.

Prevention and Treatment

Prevention of heat exhaustion requires an adequate supply of water easily accessible while working in hot climates or conditions both during and after working hours. The treatment consists essentially of rest in bed in a cool environment with a high intake of fluids. The preferable method of intake is by mouth unless the person is unconscious, then fluid replacement needs to be given intravenously. Also, the person should be kept cool until thermoregulatory system is back in balance.

Heatstroke

A stage of thermoregulatory failure with sudden onset following exposure to a hot environment with a high body temperature greater than 40.6 °C (105°F) characterized by an absence of sweating and disturbance of the central nervous system. It is frequently fatal.

Hyperpyrexia

The same symptoms as heatstroke except the patient is conscious and may be sweating. The rectal temperature will be slightly lower than that of heatstroke. Signs and symptoms: euphoria, headache, dizziness, drowsiness, numbness, restlessness, purposeless movements, uncoordinated movements, aggressiveness, mania, suicidal tendencies, mental confusion, and sudden onset of delirium or coma in heatstroke.

The following are some definitions of some terms which we have used above with which you may not be familiar:

Oliguria - Secretion of a diminished amount of urine in relation to the fluid intake.

Pyrexia - A fever, or a febrile condition; abnormal elevation of the body temperature.

Psychomotor - Pertaining to motor effects of cerebral or psychic activity.

Cognitive Functioning (Cognition) - The operation of the mind by which we become aware of objects of thought or perception, including understanding and reasoning.

Mania - Excitement manifested by mental and physical hyperactivity, disorganization of behavior, and elevation of mood.

Atropine

This drug is widely used in medicine today. It is the current drug of choice in countering the effects of nerve agent poisoning in the field. Its side effects are minimal at the doses to be employed

in this study. These effects are mainly those of increased heart rate, blurred vision, and dryness of mouth. The drug is well tolerated and severe responses are usually seen only at doses greater than the largest dose to be used in this study. Since individual responsiveness to any drug may vary, it is possible that some subjects may experience heightened side effects even at these low dose levels. Along with the physiological side effects of increased heart rate; blurred vision, and dryness of mouth, it is possible you may also experience some perceptual, cognitive, or behavioral side effects, such as poor coordination, shortened attention span, confusion, nausea, partial amnesia, and hallucinations. However, these side effects, if present, will be of a transient nature. I further understand that although atropine has been used extensively in clinical medical practice for the treatment of patients, it has not yet been approved by the United States Food and Drug Administration for use in the manner proposed by this research and is thus classified as an investigational drug.

It is expected that you will experience some degradation of performance due to atropine or heat stress. The safety pilot will be instructed to observe your performance and will not allow you to progress to unsafe levels of degradation. Although atropine is rapidly eliminated from the body, you will not be allowed to return to flight duty until you have been examined by the flight surgeon and your visual accommodation has returned to at least 90 percent of your preexposure value. This condition is not expected to be present beyond 48 hours past last dose.

Biochemistry

During your initial physical screening a blood sample not to exceed 30 mL (1 ounce) will be drawn for analyses. The analysis will include complete blood count, electrolytes, BUN, creatinine, liver function tests, and blood glucose. Additionally, throughout the research period you will be requested to donate urine samples for analyses. These analyses include specific gravity, dipstick screen for abnormal products (glucose, ketone, acetone, urobilinogen, blood); and catecholamine (epinephrine, norepinephrine, dopamine). There are no legal implications in the analyses of the blood or urine. There will be no drug screening on any samples without further expressed written permission from the volunteer. Each urine and blood sample is to be considered a donation for research purposes.

BENEFITS

You will gain no direct benefit from participation in this study other than knowing that you have participated in a study that will assess the effects of CW antidotes on pilots.

UNCONDITIONAL CONSENT FOR USE OF PICTURE AND SOUND

The United States Government is granted the right to use, to the extent and for the purpose it desires, any picture (still, motion, those transmitted via TV or recorded on video tape or otherwise) and sounds (vocal, instrumental, or otherwise) whether used together or separately, taken or recorded by or on behalf of the Aeromedical Research Laboratory.

(Date)

(Signature)

(Home address)

(Military address)

Above consent obtained by:

(Signature)

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BENEFITS

You will gain no direct benefit from participation in this study other than knowing that you have participated in a study that will assess the effects of CW antidotes on pilots.

DISCOMFORTS

You may be stressed and uncomfortable during this study, but we have established safety limits and the experiment will not be allowed to proceed if any of these limits are reached. By monitoring your heart rate, and rectal temperature and comparing these parameters with established limits, we will be able to terminate the experiment at a point at which you are stressed which will minimize the risk to you.

Insertion of the rectal thermometer probe can cause some discomfort. You may experience local irritation from the adhesive electrodes used for physiological monitoring.

COMPENSATION

Volunteers under the provisions of AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such projects.

For further information related to the rights of volunteer subjects, you can contact the Post Staff Judge Advocate General Office at (205) 255-3482, Building 406.

CONFIDENTIALITY

Volunteers will be photographed and recorded using still and motion photography, video equipment and magnetic tape. You will not be personally identified. Records will be permanently maintained and may be inspected by officials from the Food and Drug Administration, the U.S. Army Medical Research and Development Command and other Army agencies.

POINT OF CONTACT FOR FURTHER QUESTIONS

If you have any questions about any research procedures, feel free to contact John A. Caldwell at 255-6864 or Building 6901, Room F-11.

Volunteer's Name (Print or Type)

Volunteer's Signature

Date

I have read and signed the volunteer Agreement Explanation form. I have been given the opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights on study-related injury, I may contact the Post Staff Advocate General Office, Fort Rucker, Alabama 36362-5000, (205-255-3482). I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits; however, I may be required to undergo certain examinations if, in the opinion of the attending physicians, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

Volunteer's Name (Print or Type)

Volunteer's Signature Date

Witness's Name (Print or Type)

Witness's Signature Date

UNCONDITIONAL CONSENT FOR USE OF PICTURE AND SOUND

The United States Government is granted the right to use, to the extent and for the purpose it desires, any picture (still, motion, those transmitted via TV or recorded on video tape or otherwise) and sounds (vocal, instrumental, or otherwise) whether used together or separately, taken or recorded by or on behalf of the Aeromedical Research Laboratory.

(Date)

(Signature)

(Home address)

(Military address)

Above consent obtained by:

(Signature)

After review of medical records, subject is authorized to:
Participate freely in all tests _____
May not participate in any stress testing _____

Signed: _____ (Physician)

Date: _____

Appendix B

List of manufacturers

List of manufacturers

Apple Computer, Inc.
20525 Mariani Avenue
Cupertino, CA 95014

Asahi Optical Co, Ltd (Litemate)
C. P. O. 895
Tokyo 100-91, Japan

Audiotronics Video Display Division
8299 Central Avenue NE
Spring Lake Park, MN 55432

Bell Helicopter Textron
P. O. Box 482
Fort Worth, TX 76101

Cadwell Laboratories, Inc.
1021 Kellogg Street
Kennewick, WA 99336

Columbia Data Products, Inc.
1154-T West Highway 436
P. O. Box 3037
Altamonte Springs, FL 32714

Digital Equipment Corporation
Continental Boulevard Mk01/W83
Merrimack, NH 03054-9987

Dual Task Technologies, Inc. (ZITA)
Suite 231, 4400 East West Highway
Bethesda, MD 20814

Electronic Associates, Inc.
185 West Monmouth Parkway
West Long Branch, NJ 07764

Eli Lilly & Co.
307-T East McCarty Street
Indianapolis, IN 46285

Gould, Inc.
Medical Products Division, SRL Medical
805 Liberty Lane
Dayton, OH 45449

Grass Instrument Co.
101 Old Colony Avenue
P. O. Box 516
Quincy, MA 02169

Hartman Systems Division of ATO (DEI)
360 Wolf Hill Road
Huntington Station
Long Island, NY 11746

Hewlett-Packard Co.
3000 Hanover Street
Palo Alto, CA 94304

Hines Ophthalmic Laboratory (Worth)
Hines Contact Lens Laboratories
14 Hamilton Street
P. O. Box 1083
Ashville, NC 28802

Hittman Medical Systems, Inc. (Holter)
500 Bostwick Avenue
Bridgeport, CT 06605

Allergan Humphrey
3081 Teagarden Street
San Leandro, CA 94577

Lameris Instrumenten b.v.
Biltstraat 449
3572 aw Utrecht
The Netherlands

Loral Data Systems (Conic)
9020 Balboa Avenue
San Diego, CA 92123

Marquette Electronics, Inc.
P. O. Box 23181
8200 West Tower Avenue
Milwaukee, WI 53223

Panasonic Industrial Co.
One Panasonic Way
Secaucus, NJ 07094

Quinton Instrument Co.
2121 Terry Avenue
Seattle, WA 98121

Reuter-Stoke Canada Ltd. (Wibget)
465 Doggie Drive
Cambridge, Ontario, Canada N1R5X9

Tektronix, Inc.
P. O. Box 500
Beaverton, OR 97077

Telefactor Corporation
Union Hill Building, De Haven Street
West Conshohocken, PA 19428

Topcon Instrument Corporation of America
65 West Century Road
Paramus, NJ 07652

Sanyo Electric, Inc. (True)
1200 West Artesia Blvd.
Compton, CA 90220

Vistech Consultants, Inc.
1372 N. Fairfield Road
Dayton, OH 45432

Yellow Springs Instrument Co.
P. O. Box 279
Yellow Springs, OH 45387