



**Effects of the Chemical Defense
Antidote Atropine Sulfate
on Helicopter Pilot Performance:
A Simulator Study**

By

**Ronald R. Simmons
John A. Caldwell
Robert L. Stephens
Lewis W. Stone
David J. Carter
Isaac Behar
Glenn W. Mitchell
Francis S. Knox, III
Heber S. Jones
Philip L. Taylor**

Biomedical Applications Research Division

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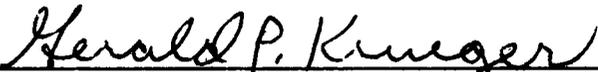
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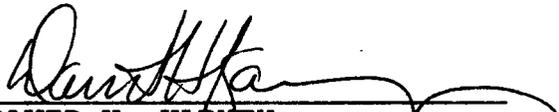
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Reviewed:


GERALD P. KRUEGER, Ph.D.,
LTC, MS
Director, Biomedical Applications
Research Division

Released for publication:


J.D. LaMOTHE, Ph.D.
COL, MS
Chairman, Scientific
Review Committee


DAVID H. KARNEY
Colonel, MC
Commanding

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in flight performance resulted from a slowing of both information processing and psychomotor performance. Atropine effects were not of sufficient magnitude to preclude further research under actual flight conditions.

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Notes

Mr. Ronald R. Simmons and CW4 (ret.) David J. Carter now are with:
Universal Energy Systems
50 Donnell Blvd
Daleville, Alabama

LTC (ret.) Philip L. Taylor now is with:
Dylantic, Inc.
Virginia Beach, Virginia

LTC Glenn W. Mitchell now is with:
Uniformed Services University of the Health Sciences
Washington, D.C.

Dedication

COL Edward L. Buescher, MC (1925-1989) was considered by many to be a major force behind modern research on atropine in the military. He influenced many researchers in the U. S. Army Medical Research and Development Command to conduct studies such as the one reported here to answer applied operational questions, and to ensure we had baseline data against which to judge effects of future chemical defense antidotes.

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In a study as extensive as this one, many people beside the authors were involved. The authors take this opportunity to recognize them:

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- Ms. Gloria Kennedy made arrangements for all selected subjects and typed the final manuscript;
- Mr. Alan Lewis wrote much of the software for the physiological data collection;
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- SGT Debra Rushing supervised the many months of technician activities;
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- CPT Scott Wells and CW4 Neil Clark were the two safety pilots

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Introduction

Statement of the problem

Aviators must maintain high levels of vigilance and skill to safely and effectively accomplish flight missions. Performance requirements of air-based operations differ markedly from ground operations. Clearly, aviation poses numerous concerns with regard to the possible deleterious effects of any substance pilots encounter which may potentially cause performance impairments. The effects of atropine sulfate given as a chemical warfare antidote in the doses prescribed by U.S. Army training doctrine have not been documented within an aviation context. It is essential that safety concerns over its use be examined.

At the same time, performance and physiological effects of antidote and pretreatment drugs on aviators must be determined through systematic research--first, using controlled, simulated flight conditions; then, if safety permits, using in-flight validation of those effects during simulated missions.

Background

Occurring naturally in the plant Atropa belladonna, atropine is used therapeutically for a variety of functions such as reduction of bronchial secretions during surgery and dilation of pupils during eye exams. Also, atropine is commonly employed to ameliorate symptoms of organophosphate poisoning (sometimes encountered when using certain insecticides and always a threat where chemical nerve agents are found). This wide range of uses has led to atropine being extensively studied and its physiological effects being reasonably well documented. Since its isolation in 1831, physicians have had substantial experience administering the drug (Weiner, 1980). Its widespread use in clinical medicine is attested by the many available pharmaceutical preparations containing atropine either alone or in combination with other drugs.

A brief discussion will explain the importance of atropine in the military environment. The body prevents accumulation of excess acetylcholine (a major neurotransmitter in the central nervous system) by destroying it with the enzyme acetylcholinesterase. Nerve agent blocks the action of acetylcholinesterase, allowing accumulation of acetylcholine and overstimulation of the target organs, producing the signs/symptoms shown in Table 1. Atropine blocks the action of acetylcholine and prevents overstimulation, even in the presence of excess acetylcholine. In this way, injection of atropine after exposure to nerve agent prevents many of the effects of nerve agent poisoning--breathing impairment being one of the exceptions. For small amounts of

Table 1.

Signs and symptoms of acetylcholine excess following systemic absorption

=====

A. Muscarine-like:

Bronchial tree-----Tightness in chest, with prolonged wheezing expiration suggestive of bronchoconstriction or increased secretion, dyspnea, slight pain in chest, increased bronchial secretion, cough, pulmonary edema, cyanosis.

Gastrointestinal----Anorexia, nausea, vomiting, abdominal cramps, epigastric and substernal tightness (cardiospasm) with "heartburn" and eructation, diarrhea, tenesmus, involuntary defecation.

Sweat glands-----Increased sweating.

Salivary glands-----Increased salivation.

Lacrimal glands-----Increased lacrimation.

Heart-----Slight bradycardia.

Pupils-----Slight miosis, occasionally unequal, later maximal miosis (pinpoint).

Ciliary body-----Blurring of vision.

Bladder-----Frequency, involuntary micturition.

B. Nicotine-like:

Striated muscle-----Easy fatigue, mild weakness, muscular twitching, fasciculations, cramps, generalized weakness, including muscles of respiration, with dyspnea and cyanosis.

Sympathetic ganglia-Pallor, occasional elevation of blood pressure.

C. Central nervous system:

Giddiness, tension, anxiety, jitteriness, restlessness, emotional lability, excessive dreaming, insomnia, nightmares, headaches, tremor, withdrawal and depression, bursts of slow waves of elevated voltage in EEG, especially on overventilation, drowsiness, difficulty concentrating, slowness on recall, confusion, slurred speech, ataxia, generalized weakness, coma, with absence of reflexes, Cheyne-Stokes respirations, convulsions, depression of respiratory and circulatory centers, with dyspnea cyanosis, and fall in blood pressure.

=====

Note: This table was reproduced from TM 8-285 (U. S. Department of the Army, 1974).

chemical agents, this breathing impairment may not be a problem. However, for larger doses, breathing assistance may be critical. (A more in-depth background of atropine is included in Appendix A.)

Military significance

Recent intelligence and published changes in Warsaw Pact military doctrine have led analysts to believe there is a high probability an enemy will use chemical and biological agents in future armed conflicts. Thus, the threat of chemical weapons, as well as both conventional and nuclear weapons, is considered in U. S. military doctrine. Public attention focused on chemical deployment and its use by the Soviets and their counterparts in Southeast Asia and Afghanistan (Haig, 1982) and, more recently, in the war between Iran and Iraq (Newhouse, 1987).

Army aviators are at serious risk in the chemically contaminated environment since even nonlethal riot control agents such as tear gas 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 the cockpit to don a chemical defense (CD) protective clothing ensemble necessitate that in any chemical threat situation, the pilot must previously have donned the clothing. Thus, the ability of the pilot to effectively operate his aircraft while in a CD 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 it been determined whether or not the antidotes are safe for aviators to use.

Three compounds--atropine sulfate, pralidoxime chloride (2 PAM-CL), and pyridostigmine bromide--currently are under consideration by the military as APD; but, each drug has 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. On page 69 of their report, Taylor et al. (1985)--having used general aviation pilots in a fixed-wing simulator--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)...."

This is a report of the first phase (using a helicopter flight simulator) of a continuing study to determine the effects of atropine on helicopter pilots in actual flight scenarios. If determined safe, a replicate second phase will follow using an actual helicopter. Such research is of critical importance to strategists, tacticians, and commanders who must plan for battles which may be fought under chemical warfare conditions. 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 performance of Army helicopter pilots who were voluntarily administered the chemical defense antidote atropine sulfate. The primary focus was to determine the effects of unchallenged¹ doctrinal doses (2 and 4 mg injected intramuscularly (i.m.)) of atropine on the efficiency of pilots while accomplishing tasks required by operational flight scenarios in a flight simulator. In addition, some psychomotor, cognitive, physiological and psychological effects of atropine were examined.

Method

Subjects

Twelve male Army helicopter pilots in good health served as subjects. Each possessed at least 20/20 uncorrected vision and normal hearing and passed a comprehensive medical examination which included a cardiac stress screen. In addition, each subject was tested for atropine sensitivity prior to participation. All participants were qualified in the U. S. Army's UH-1 utility helicopter.

Subjects ranged in age from 21 to 32 with a mean age of 27. Previous flight time experience ranged from 184 to 3000 hours with a mean of 667 flight hours. Two of the subjects had in excess of 1100 hours; seven had over 400 hours, but less than 1100 hours; and the remaining three aviators had less than 400 flight hours.

¹In this context, "unchallenged" refers to a situation in which atropine is used when there has been no exposure to a chemical agent. This might be brought about, for example, if a pilot flies through a cloud of battlefield vapors, suspects exposure to a chemical agent, and injects atropine sulfate when in fact the cloud was harmless smoke, not a chemical agent threat.

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 3.0 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 dose consisted simply of sterile water for injection, U.S.P. Once again, the injection volume was 1.0 ml.

Respiration

During the flight simulator portion of the study, respiration was recorded with an impedance pneumograph to allow respiratory modulation of heart rate to be identified in a concurrent study of heart rate spectra. These data were collected for safety purposes and will not be discussed further; however, they will be reported when the study of that developmental heart rate analysis technique is complete.

Urine specific gravity

Urine was collected and measured for volume and specific gravity using an American Optical refractometer manufactured by Cambridge Instruments*. These data were gathered to monitor the hydration of each subject throughout the protocol.

Electrocardiography (ECG)

A continuous electrocardiographic recording was made from three ECG chest leads attached to a Holter* monitor. During simulator flight, the Holter recorder was replaced with a Digital Equipment Corporation (DEC)* PDP 11/03-based acquisition system which digitized the ECG, and then computed and scored interbeat

*See Appendix B.

intervals. Heart rate also was displayed continuously on a CRT monitor. The ECG data were used both to demonstrate the presence of significant drug levels in the blood and to ensure the safety of research participants.

Visual accommodation

The ability of the subject to focus his eyes on near objects was measured at various times throughout the test day with a standard Prince rule (a card with small print mounted on a slide on a calibrated stick.) This measure provided an indication of how well the subject was able to adjust the thickness of the lenses of his eyes to accommodate for near vision in the cockpit.

Helicopter flight simulator

All missions were flown in the U. S. Army Aeromedical Research Laboratory (USAARL) flight simulator (Figure 1), a replica of the U. S. Army's UH-1 utility helicopter cockpit with a two degree-of-freedom (pivotal) motion system. The flight dynamics were patterned after the aerodynamics of the UH-1 and controlled by a closed loop analog computer. A DEC LPA-11K microprocessor subsystem digitized the analog signals. Up to 64 channels of information at a sampling rate of up to 20 per second were collected and transmitted to a DEC VAX 11/780 computer using a variety of signal buffers and amplifiers connected to an EAI* 681 analog computer (Figure 2) used for signal conditioning. Specialized software provided real-time processing capability. The acquisition program performed calibration of flight parameters, verification of simulator status, sequencing of flight maneuvers, display of flight parameters, storage of relevant flight parameters, and storage of markers used to delimit the beginning and end of each maneuver.

Contrast sensitivity function (CSF)

A Nicolet* Optronics CS2000 contrast sensitivity test system was used to evaluate spatial vision by providing an indication of the spread of the retinal image affected by such factors as pupil size, accommodation, and the integrity of the retinal mosaic. The system consisted of a microprocessor-controlled video display generator and data acquisition system. The mean luminance of the video display was 26.5 fL which is at the low photopic level. At the 10-foot viewing distance, the overall display subtense was 4.4 by 5.6 degrees. The display was surrounded by a high-intensity (4300 fL) fluorescent lamp masked so no direct light reached the display screen. The test room was entirely black, with dim room illumination provided by incandescent lamps recessed into the ceiling.



Figure 1. U. S. Army Aeromedical Research Laboratory helicopter flight simulator.



Figure 2. EAI 681 analog computer used for signal conditioning.

Performance assessment battery (PAB)

Selected subtests from the performance assessment battery developed by personnel in the Division of Neuropsychiatry, Walter Reed Army Institute of Research (WRAIR) were administered to each subject to assess possible psychological or cognitive changes during the course of the study. The equipment consisted of an Apple* II+ microcomputer equipped with an external, lap-held, standard "QWERTY"-configured keyboard, a hand-held stimulus display/response panel, and an external CRT monitor. All tests were administered in a shielded, sound-attenuated chamber (1.98 m X 1.82 m X 1.92 m) dimly illuminated by a single 40-watt incandescent bulb.

Zero input tracking analyzer (ZITA)*

The zero input tracking analyzer (model Mk Xc), a programmable, dual-task compensatory tracking device, presented a fixed target and a horizontally 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 additionally was equipped with two small pushbuttons used as response keys for a secondary auditory distraction task. The ZITA was administered to each subject to detect the effects of atropine on first order (velocity), second order (acceleration), and third order (jerk) tracking ability. The entire process, from training to data storage, was controlled by another Apple II+ microcomputer. All tests were presented in a shielded, sound-attenuated chamber (identical to the one used for the PAB except for lighting) dimly illuminated by a single 25-watt incandescent bulb.

Visual evoked potential (or response) (VEP)

A Cadwell* 7400 visual evoked response (VEP) collection system connected to a microcomputer controlled presentation of visual stimuli on a CRT and collected and stored evoked response data. The VEP was employed in two basic forms to detect changes in evoked responses as a result of drug exposure. The first form of the task consisted of presentation of black-and-white checkerboard patterns on a 15-inch CRT located in a sound-attenuated chamber similar to the ones used for the PAB and ZITA. The patterns (4 x 4, 8 x 8, 16 x 16, 32 x 32, 64 x 64, and 128 x 128 squares) were reversed at a rate of 3.75 Hz, and a total of 100 responses were averaged under each stimulus pattern. Electrode configuration for the sampled channel (using the International 10-20 system) was Oz

referenced to Fz and grounded to A1 or A2. The second form of the task consisted of the presentation of a 4 x 8 checkerboard pattern which reversed approximately 26 times out of 200 sweeps. Subjects counted each reversal by pressing a handheld pushbutton. Electrode placement for the sampled channel was Pz referenced to A2 and grounded to Fz.

The high-pass filter of the system was set at 100 Hz, while the low-pass filter was set at 1 Hz; neither the automated artifact rejection option nor the 60 Hz notch filter were used while collecting data.

Procedure

General

Each subject arrived at the Laboratory on Sunday of the testing week prepared to remain in the Laboratory for a full 6 days. The project was fully described; voluntary consent forms were completed; and a physical examination, cardiac stress evaluation, and atropine sensitivity test were performed. Following the initial evaluation and placement of scalp electrodes, telemetry equipment was checked for proper operation and each subject was given two series of training sessions on all of the performance tests separated by a familiarization flight in the simulator. (See Table 2.)

Table 2.

Schedule for training day (Sunday)

```
=====
1100 In briefing
1130 PAB
1210 Medical screening
1400 PAB and ZITA
1600 Simulator orientation
1730 Supper
1745 PAB and ZITA
1930 Eye test and contrast sensitivity
2030 VEP
2130 Release
=====
```

Testing began on Monday when the first dose of atropine was to be administered. The basic design consisted of a single training

day followed by pairs of test (or dose) and control days (see Tables 3 and 4, respectively). There was a total of 3 test days to allow 1 day for each level of atropine injection (0 mg, or saline placebo; 2 mg; and 4 mg), and a maximum of 2 control days to allow time for the atropine to be completely metabolized prior to the next dose day. The placebo day was not followed by a control day, since there was no drug present to clear from the subject's system. Dosage orders were counterbalanced (except as noted in Table 5) and randomly assigned to each subject.

Table 3.

Schedule for test (or dose) day

0530	Wake-up
0615	Urine
0630	Exam - Physiological monitors/ accommodation and ECG hookup
0700	Breakfast
0720	VEP
0745	Contrast sensitivity
0820	PAB and ZITA
0915	Break
0935	Physiological setup (at simulator)
0954	Accommodation
0955	Dose (in simulator)
1010	Flight
1140	Break
1200	VEP
1230	Contrast sensitivity
1300	Urine
1305	Accommodation
1310	PAB and ZITA
1410	Lunch
1435	Physiological setup (at simulator)
1450	Flight
1625	VEP
1650	Contrast sensitivity
1720	Urine
1725	Accommodation
1730	PAB and ZITA
1830	Supper/rest
2000	Exam
2100	Urine
2115	Personal hygiene
2145	Retire

Table 4.

Schedule for control day
(day following substantive dose day)

```

=====
0600 Wakeup
0615 Urine
0630 Examination of physiological monitors
0700 Breakfast
0720 VEP
0745 Contrast sensitivity
0820 PAB and ZITA
0915 Break
0930 Urine
0935 Physiological setup (at simulator)
0955 Flight
1115 Break
1130 VEP
1200 Contrast sensitivity
1225 Urine
1235 PAB and ZITA
1335 Lunch/free
2145 Retire
=====

```

Table 5.

Dose administration sequence

```

=====
Subject          Day (after training)
                1          2          3          4          5
-----
1                4 mg      Control  Placebo  2 mg      Control
2, 7, 8         Placebo  4 mg      Control  2 mg      Control
3, 10           4 mg      Control  2 mg      Control    Placebo
4, 11           2 mg      Control  4 mg      Control    Placebo
5, 9            Placebo  2 mg      Control  4 mg      Control
6, 12           2 mg      Control  Placebo  4 mg      Control
=====

```

Note: Due to an oversight during the progress of the study, the 0-4-2 sequence was given three times and the 4-0-2 sequence only once.

The subject was not told of the administration sequence. All injections were given by a flight surgeon, but only after the subject was prepared and all medical monitoring equipment was attached and functioning properly. The medical officer remained in the presence of the research subject (outside the simulator) for at least 30 minutes following injection. Heart rate, ECG, and respiratory rate were monitored electronically during the entire test period.

Each dose day was divided into three data-collection sessions. The first session of the day (baseline) began at approximately 0720 and consisted of administration of the VEP, CSF, PAB, and ZITA. A short break followed. The second session began with a 0955 injection followed by a simulator flight of 90 minutes duration and ended with administration of the VEP, CSF, PAB, and ZITA. Following a lunch break, the third session of data collection was run, to include all the tasks from simulator flight through ZITA (as in session two). Details of each test administration procedure are presented below.

Research areas

Physiological measures

Physiological aspects of atropine administration are reviewed in the appendix and are well described in the literature (for example, Weiner, 1980). The effects studied here were focused on volunteer safety and confirmation of predicted behavior of the monitored parameters.

The physiologic status of the subjects was monitored during all days of the study to ensure the health and safety of the subjects. The techniques were essentially those used previously (Knox et al., 1982; Mitchell et al., 1986) in studies of chemical defense ensembles. The monitoring system used here included instruments to measure heart rate, electrocardiograms (ECG), respiration and wet bulb globe temperature (WBGT). Heart rate was extracted from ECG with a digital tachometer circuit. During the simulator flight, the information on heart and respiratory rate and WBGT were available continuously to the medical observer via cathode ray tube (CRT) display.

The medical observer monitored the vital signs to determine if the subject was nearing or exceeding the physiological limits established to protect his health and safety. These limits were: heart rate > 150 beats per minute for 15 minutes. Respiration was monitored, but no a priori limits were set because breathing patterns are complex combinations of rate and flow which change continuously to assist in maintaining the body's internal pH at its normal level.

Heart rate

Each subject had three adhesive ECG chest leads attached to his torso in a modified lead IV configuration. The ECG was displayed continuously on the experimenter's screen for the purpose of medical monitoring. After the subject entered the cockpit, he was monitored for 10 minutes to establish a stable baseline prior to receiving the scheduled dose. Following dose administration, the subject was monitored continuously throughout the flight.

Urine specific gravity

Subjects were instructed to urinate in separate plastic specimen bottles each time they voided. Each specimen was labeled immediately; the specific gravity was determined; four molar hydrochloric acid was added as a preservative; and each specimen was quick frozen at -40° C. As a check on health and safety of the subjects, results of these analyses were monitored throughout the experiment for significant changes, especially those which might reflect dehydration.

Visual accommodation

The measurement of accommodation was performed only as a demonstration effort in this phase. The subject's eye accommodation was assessed at irregular intervals because of differences in processing times for other tests. Each of the subject's eyes was patched in turn as the subject was required to bring a standard target containing fine print toward the unpatched eye until the print was reported to be unreadable. Then, the distance between the target and the inferior orbital edge of the eye was measured in centimeters directly from the scale on the rule.

Flight simulator

The simulated flights consisted of components of a standard instrument flight (which included an instrument takeoff, navigation and flight to a destination airport, holding at the instrument landing system (ILS) approach outer marker, and an ILS approach to published ceiling and visibility minimums²) and a

²The "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.

series of precision instrument flight maneuvers. A safety pilot (not necessarily the same one from flight to flight) performed copilot duties and rated each subject pilot's flight performance using a rating system based on the 1984 U. S. Army aircrew training manual (ATM) standards.

The safety pilot rated the subject pilots' performance on each of four flight performance segments (instrument takeoff, level flight, holding, and instrument landing system), and produced a composite score labeled "total flight performance" for each of the six simulator flights. The first four possible ratings ranged from one to five, with five being a perfect score. The last score was a numeric total of the first 4 ratings and, thus, potentially ranged from 4 to 20, with 20 being a perfect score.

The precision maneuvers consisted of subjects performing a single iteration of a series of flight tasks (called a HAAT maneuver) which entailed flying specific headings, altitudes, and airspeeds for specified time intervals (Hamilton, Folds, and Simmons, 1982) during nine consecutive trials. All four parameters were read to the subject by the safety pilot. On a given trial, the safety pilot might instruct the subject to "fly heading, one-eight-zero degrees; altitude, 900 feet; airspeed, 80 knots; time, 20 seconds"; after which the subject could either request the instructions be repeated or indicate he understood the instructions by saying "roger." After acknowledging the instructions, the subject would first establish the flight parameters, then say "start," and then attempt to maintain the parameters for the specified time interval (the interval was judged by the subject.) When the subject indicated the specified interval had elapsed by saying "stop," the next trial would begin. Upon completion of all nine trials, control of the simulator was returned to the safety pilot.

Parameters used in the HAAT maneuver were designed to be compatible with readability of indexes and markings on aircraft instruments, gages, and dials. For example, heading was always a multiple of 5 degrees, altitude was a multiple of 20 feet, and airspeed was always a multiple of 5 knots. The pattern of parameter changes was altered in each series of three trials. In the first three trials, the heading parameter changed while the altitude and airspeed remained the same. During trials 4, 5, and 6, both the heading and the altitude changed while airspeed remained constant. During trials 7 through 9, all three parameters changed. The time interval specified for each trial was changed also. The magnitude of each change remained constant across each trial for both heading (for instance, a 60-degree turn was specified each time) and direction of altitude change (the altitude change in trial 8, for example, was always a 240-foot climb and never a descent.) Further, the combination of changes was designed so one did not aid the other (e.g., descent was not associated with airspeed increase and climb was not associated

with airspeed decrease.) The turn maneuvers incorporated 180 degrees of turn and a climb or descent of 500 feet. A standard turn rate of 3 degrees per second and a climb or descent rate of 500 feet per minute were used.

Upon completion of the HAAT maneuvers and the climb and descent, the simulator was re-established on the ground at the airfield runway. The pilot then began a standard instrument cross-country flight with an instrument takeoff. The flight included both radio and radar-assisted navigation. The level flight maneuver was a 2-minute segment of this instrument flight which was selected out of the overall straight and level at 70 minutes after the initial takeoff. Thus, the subject was not told explicitly to perform 2 minutes of straight and level. The ILS maneuver was an instrument approach to published minimums initiated 100 minutes after initial takeoff and was the termination point of the flight profile (the end of the simulator session).

On the first day, for orientation purposes, the subject was given a familiarization flight in the simulator. Thereafter, there were two flights per day on each test day (one immediately postdose at 1010 and one at 1450). There was one flight per day on each control day (at 0955.)

Contrast sensitivity function (CSF)

One purpose of the study was to provide a more comprehensive evaluation of the effects of atropine on the CSF than had been done previously. In addition to measurements obtained under normal laboratory viewing conditions, CSFs were determined with the introduction of a glare source both to enhance sensitivity to detect small visual losses and to simulate more closely the visual stressors of some operational flight conditions.

Visual contrast thresholds were obtained for sinusoidal gratings at six spatial frequencies: 0.5, 1, 2, 4, 8, and 16 cycles per degree (cpd). Each contrast threshold was measured using an ascending method of limits, the psychophysical procedure most often used to obtain a CSF (Moffitt and Genco, 1985.) On each trial, the display contrast began near zero and increased uniformly under computer control at a rate at which 50 percent contrast would be reached in 45 seconds. The subject's task was to depress a response switch immediately upon detecting the emergence of a grating pattern on the display screen. In the Sunday training session, the subject received verbal instructions, 5 preview trials in which he could observe the grating patterns emerge and attain suprathreshold contrast, and 18 practice trials consisting of 3 trials at each of the 6 test spatial frequencies in an intermixed quasi-random order (constrained so each spatial frequency occurred once in each 6-trial block.) Then, the series

was repeated with a glare source turned on to provide practice under both illumination conditions.

On dose days, CSFs were determined three times: once prior to injection (at 0745), and twice following injection (at 1230 and at 1650.) On control days, CSFs were determined at 0745 and 1200 only. In each test session, the subject received 5 warm-up trials (one trial each at 0.75, 1.5, 3, 6, and 12 cpd in random order) to allow the eyes to adapt to the prevailing illumination, followed by a quasi-random series of the 36 trials consisting of 6 trials at each of the test spatial frequencies, 0.5 to 16 cpd. Following a short break, this 41-trial set was repeated with the glare source turned on. For each subject, the mean log threshold contrast was calculated for each spatial frequency under each illumination condition. If the associated standard deviation equaled or exceeded 0.186, the cutoff for the most extreme 10 percent, it was an indication an outlier (resulting from premature responding through anticipation or delayed responding due to inattentiveness) may have existed among the six estimates of the contrast threshold, and the median was substituted for the mean.

Performance assessment battery (PAB)

Selected subtests of the WRAIR PAB (Thorne et al., 1985) were administered in this experiment to evaluate changes in cognitive performance as a result of atropine administration. The entire battery was relatively short and was administered and scored by computer. During the familiarization session on Sunday of the testing week, the test administrator read a prepared script to the subject and allowed him to view a sketch of the CRT display which would accompany each subtest. Following each explanation, the subject was tested on that particular subtest while having access to the written instructions reviewed earlier. Item-by-item feedback was given during the training session, but not during actual testing. At the conclusion of each test session, subjects were allowed to review their respective performance scores. PAB testing took approximately 30 minutes per session; there were three sessions per dose day (at 0820, 1310, and 1730) and two sessions per control day (at 0820 and 1235.) The battery consisted of the following subtests presented in the same order, each session beginning with the mood scale and ending with the four-choice reaction time (RT) test:

Mood-activation scale

Subjects rated, on a scale of 1-5, how 65 individually presented adjectives reflected their current mood and activation.

Six-letter search

A string of 6 letters appeared at the top of the CRT screen and a string of 20 letters appeared at the middle of the screen. Subjects were to indicate as quickly and as accurately as possible whether or not all letters from the first string were present in the second string by pressing the "S" (same) key if all letters in the first line were present in the second line or by pressing the "D" (different) key if any of the first 6 letters were absent in the 20-letter string.

Logical reasoning

A letter pair, "BA" or "AB," appeared on the screen along with a statement which described a sequential relationship between the two letters. Subjects were to determine as quickly and as accurately as possible whether or not the statement was a correct description of the letter positions as displayed. The response was a press of the "S" key if correct or the "D" key if incorrect.

Digit recall

A string of 9 digits was presented for 1 second, followed by a 3-second blank screen, followed by a string of 8 digits (in different order from the string of nine.) Subjects were to indicate which one of the digits presented in the first string was missing from the second string by entering that digit on the number keypad.

Serial addition/subtraction

Two single-digit numbers followed by either a plus or a minus sign were presented rapidly and sequentially on the screen. Subjects were to perform mentally the indicated operation in the sequence given. If the resultant answer was a positive number greater than 9, they were to subtract 10. If the answer was less than 0, subjects were to add 10 (thus making all responses in the range from 0 to 9.) They were to enter the single digit answer on the number keypad.

Four-choice serial reaction time (RT)

Subjects were given a hand-held stimulus/response panel arrayed with four light-emitting diodes (LED) arranged in a square situated above four response keys arranged in the same pattern as the LEDs. Subjects were to respond as quickly as possible to each LED stimulus by pressing the response key corresponding to the position of the illuminated LED.

Zero input tracking analyzer (ZITA)

Fine motor coordination and ability to respond to concurrent tasking were measured using the ZITA because it offered capabilities to present a variety of increasingly difficult, single-dimension tracking tasks to evaluate simple tracking performance alone or under the distraction contributed by a secondary auditory task.

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). Using a joy stick, subjects were to keep the cursor as close as possible to a triangle-shaped target in the center of the display. The motion characteristics of the cursor changed from one level of difficulty to another depending on the program. In task level 1, the program moved the cursor uniformly across the screen (constant velocity). The cursor responded almost immediately to any reversal of the joy stick. In task level 2, the program introduced a linear change of velocity (acceleration) of the cursor. A joystick reversal decelerated the cursor at the same rate before reversing it.

In task level 3, the program uniformly changed the rate of acceleration (jerk) of the cursor. 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 he also had to anticipate and enter the joystick manipulations required to keep it there.

To further increase the demands of ZITA, the subject was intermittently (with his knowledge) presented with a secondary auditory distraction task (ADT). While still performing the primary tracking task, he was to respond to either of two randomly presented tones by pressing one of two buttons (depending on the frequency of the tone). The difficulty of the ADT was controlled by changing the number of tones presented per unit of time. At the lowest difficulty level, the subject received no tones (ADT0). At the moderate difficulty level, he received 1 tone every 2 seconds (ADT2); whereas, at the highest difficulty level, he received 1 tone every second (ADT1).

Each subject was trained initially to operate the ZITA on the first training day using a procedure recommended by the ZITA's designer (Walker, n.d.). No attempt was made to train to asymptote. The session consisted of a 14-trial interactive sequence

with an experimenter. All subjects used their right hands to operate the joystick (just as they would in the aircraft, regardless of their handedness) and their left hands to respond to the auditory distraction task. They operated Tasks 2 and 3 for 60 seconds each and Task 1 for 30 seconds³.

Immediately following the initial training session, the subject previewed the 19-trial testing sequence with the experimenter available in case of questions. About 2 hours later, he previewed the test sequence again. For training and all subsequent sessions, the subject was seated at a table in a dimly lit 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. At the conclusion of each run, the subject was presented with performance feedback along with parameters for the next run which were presented on the CRT.

Additionally, at the conclusion of each session, the subject was shown a listing of all scores attained during the session. There were two ZITA sessions per control day (0850 and 1305) and three sessions per dose day (one predose at 0850, and two postdose at 1340 and 1800.) During test sessions, the door to the testing chamber remained open and an experimenter was present outside at all times. The test sequence of 19 runs remained constant across all sessions.

Visual evoked potential (or response) (VEP)

Visual evoked response paradigms were included to evaluate the effects of atropine on CNS activity and the visual system. Scalp electrodes were placed at F7, F8, T3, T4, T5, T6, Oz, Pz, and either A1 or A2 locations using the International 10-20 system; however, most of these sites were used only for general monitoring through telemetry. Only the ones specified earlier were monitored during the VEP. Sites were thoroughly cleaned, after which Grass* silver cup electrodes were affixed to the scalp using collodion. To collect these data, two different tasks were employed: The first was designed simply to elicit the early, "recognition" components of the VEP. Subjects passively observed a CRT display during 100 sweeps of checkerboard pattern reversals ranging in size from 4 x 4 squares to 128 x 128 squares. The second task was designed to elicit the later, "decision" component of the VEP. Subjects were instructed to once again observe the CRT during 200 sweeps of sampling while a 4 x 8 pattern reversed approximately 15 percent of the time. This time, however, they were to press a

³Task 1 calls for a rapid and persistent "jiggling" motion which quickly results in muscle fatigue.

handheld pushbutton connected to a counter when each pattern reversal occurred.

Subjects were trained on both of these tasks on Sunday of the testing week. Then the tasks were administered three times on each dose day (once prior to the injection, at 0720, and twice following injection, at 1200 and 1625); and twice on each control day (at 0720 and 1130).

Results

Most of the analyses used to determine the effects of atropine on performance were accomplished with repeated measures analysis of variance, BMDP4V (Dixon et al., 1983). Where violations of the sphericity assumption were found (indicated by Box/Geisser-Greenhouse estimated epsilon values less than critical values), Box/Geisser-Greenhouse corrected degrees of freedom were used (Grieve, 1984).

Physiological measures

Heart rate

Heart rate plotted as a function of time for 2 mg (Figure 3) and 4 mg (Figure 4) showed the characteristic initial bradycardia shortly after injection, followed by tachycardia. The lower curve in each figure shows a decrease in the variability of heart rate (decreased standard deviation) as atropine exerted its influence. Table 6 summarizes the means and standard deviations for the heart rate at four key points for all drug levels during both flights.

Considering each flight separately and both flights together, there were no significant differences in heart rate between any of the reference points at the placebo (baseline) level. At the heart rate baseline point (HRBL), there was a dose X flight interaction ($F(2,22)=5.56$, $p=0.0111$) precipitated by a still slightly elevated heart rate (79.4 bpm) at the beginning of the afternoon flight on the 4 mg day. Neither dose nor flight main effects were significant.

At the minimum heart rate point (HR Lo), there was the expected interaction between dose and flight ($F(2,22)=41.92$, $p<.0001$), which simple effects analysis identified as coming from flight differences at 2 mg and 4 mg and dose differences in the morning flight (Table 6). The differences between placebo and each drug dose were significant ($p<0.0001$), but not significant when 2 and 4 mg were compared to each other. Both dose and flight

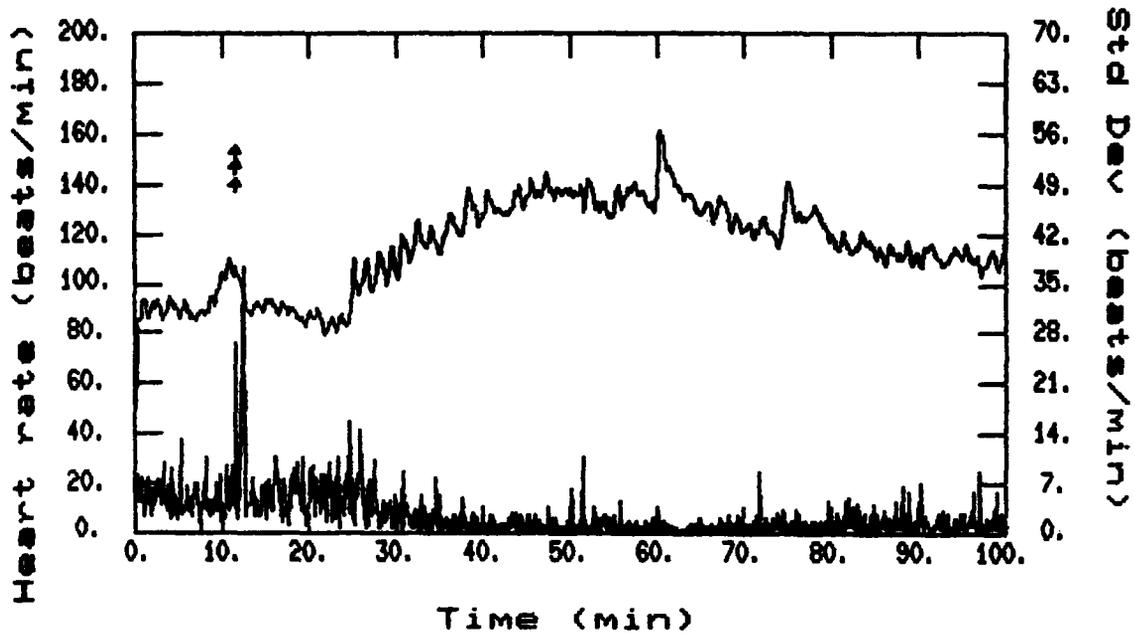


Figure 3. Heart rate plotted as a function of time for 2 mg atropine.

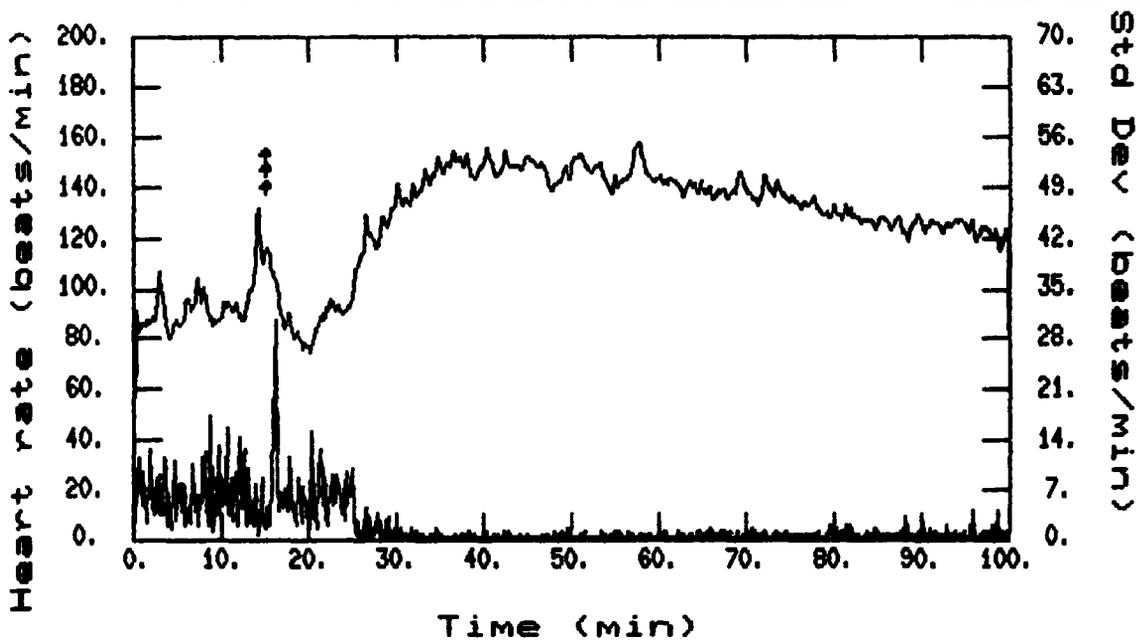


Figure 4. Heart rate plotted as a function of time for 4 mg atropine.

Table 6.

Heart rate data

Dose		HRBL	HR Lo	HR Hi	HR@60	SD@60
<u>For morning flights:</u>						
0 mg	Mean	75.6	75.7	75.7	74.6	3.9
	SD	13.0	13.1	13.1	13.8	1.0
2 mg	Mean	72.4	64.7	121.2	110.8	1.5
	SD	11.7	11.1	13.9	9.4	0.8
4 mg	Mean	71.9	62.0	133.6	116.5	1.7
	SD	11.4	8.3	17.9	12.9	1.7
<u>For afternoon flights:</u>						
0 mg	Mean	72.7	76.0	76.0	75.4	3.7
	SD	10.3	11.3	11.3	11.9	1.2
2 mg	Mean	76.1	75.2	75.2	75.1	4.5
	SD	14.1	9.4	9.4	7.9	1.4
4 mg	Mean	79.4	77.3	77.3	74.5	3.9
	SD	11.0	8.3	8.3	9.8	1.2

Note: HRBL = baseline heart rate in bpm
 HR Lo = minimum heart rate after injection
 HR Hi = maximum heart rate after injection
 HR@60 = heart rate 1 h after injection
 SD@60 = variability in heart rate at 1 h
 after injection

main effects were significant ($F(2,22)=11.83$, $p=0.0003$ and $F(2,22)=56.76$, $p<0.0001$; respectively) and followed the same pattern.

Peak rates (HR Hi) followed the same pattern as the lows, except this time the difference between 2 and 4 mg in the morning was significant ($F(2,22)=10.51$, $p=0.0078$).

The pattern for rates at 60 minutes post dose (HR@60) was identical to that of the lows; the difference between 2 mg and 4 mg in the morning was not significant. The standard deviation of heart rate, a measure of within subject variability, at 60 minutes post dose (SD@60) also followed that pattern (i.e., a significant

decrease over baseline for both 2 and 4 mg, but not between each other).

Heart rates were measured in a different way during the afternoon flights and during all nondrug flights because there were no characteristic lows or highs to trigger the algorithm. During those flights, the HR Lo and HR Hi values were replaced with the average heart rate over the respective flight time. Compared to the morning (preinjection) baseline (HRBL) at each level of atropine, there were no significant differences.

Urine specific gravity

Urine specific gravities varied widely for each subject during each day and across days without a demonstrable pattern. Table 7 shows the mean and standard deviation of each subject's results over the study period. (No analyzable urine was obtained from Subject 9 due to a procedural error in sample processing.) The range of values remained within normal physiological limits for all subjects. There were no instances of sequential determinations over a value of 1.030 specific gravity which would have indicated significant dehydration.

Table 7.

Urine specific gravity means
listed by subject

Subject	Mean	Standard deviation
1	1.023	0.0075
2	1.021	0.0041
3	1.011	0.0083
4	1.022	0.0046
5	1.017	0.0080
6	1.025	0.0046
7	1.009	0.0034
8	1.014	0.0056
9	(absent)	
10	1.017	0.0080
11	1.015	0.0042
12	1.012	0.0072

Visual accommodation

The observed behavior of visual accommodation tended to follow predictions from the literature previously referenced. That is, visual accommodation tended to worsen with increasing doses of atropine as expected.

Helicopter flight simulator

Subjective ratings of flight performance

Each of the five flight performance segments was analyzed separately in a 3 X 2 repeated measures analysis of variance (ANOVA) with three levels of dose (placebo, 2 mg, and 4 mg) and 2 levels of flight (morning and evening). A dose effect predominated the findings with respect to the safety pilot performance ratings. As a rule (the holding segment excepted), there were no significant differences between the placebo ratings and those at 2 mg; but, in every case, the 4 mg condition was involved in some way. In the ITO, for example, the dose effect depended on the flight (session), but still involved the 4 mg condition.

For the instrument takeoff segment, the analysis revealed a dose X flight interaction and a dose main effect ($F(2,22)=3.92$, $p=0.0350$ and $F(2,22)=5.33$, $p=0.0130$, respectively). The interaction (Figure 5) was accounted for, in part, by a significant difference between morning and evening sessions for only the 4 mg condition, ($F(1,11)=7.37$, $p=0.0201$), with pilots more often receiving lower ratings during the evening flight. Analysis of simple effects further revealed a dose effect during the evening flight which was not present during the morning flight. Contrasts indicated the pilots' evening ratings were lower for the 4 mg flight than for either the placebo flight ($F(1,11)=7.21$, $p=0.0212$) or the 2 mg flight ($F(1,11)=25.69$, $p=0.0004$). The difference between the placebo and 2 mg flights was not significant.

Contrasts for the dose main effect (Figure 6) resulted in similar findings. The 4 mg dose performance ratings were lower than those for either the placebo ($F(1,11)=5.33$, $p=0.0413$) or the 2 mg dose ($F(1,11)=8.77$, $p=0.0129$). The difference between the placebo and 2 mg flights was not significant.

Analysis of the level flight segment also revealed the existence of a significant dose main effect ($F(2,22)=7.31$, $p=0.0037$). Contrasts (Figure 7) indicated the effect was due to a difference between the 4 mg condition and the placebo condition ($F(1,11)=15.11$, $p=0.0025$) and between the 4 mg condition and the 2 mg condition ($F(1,11)=4.91$, $p=0.0487$), but not between the placebo condition and the 2 mg condition. The pilots were rated

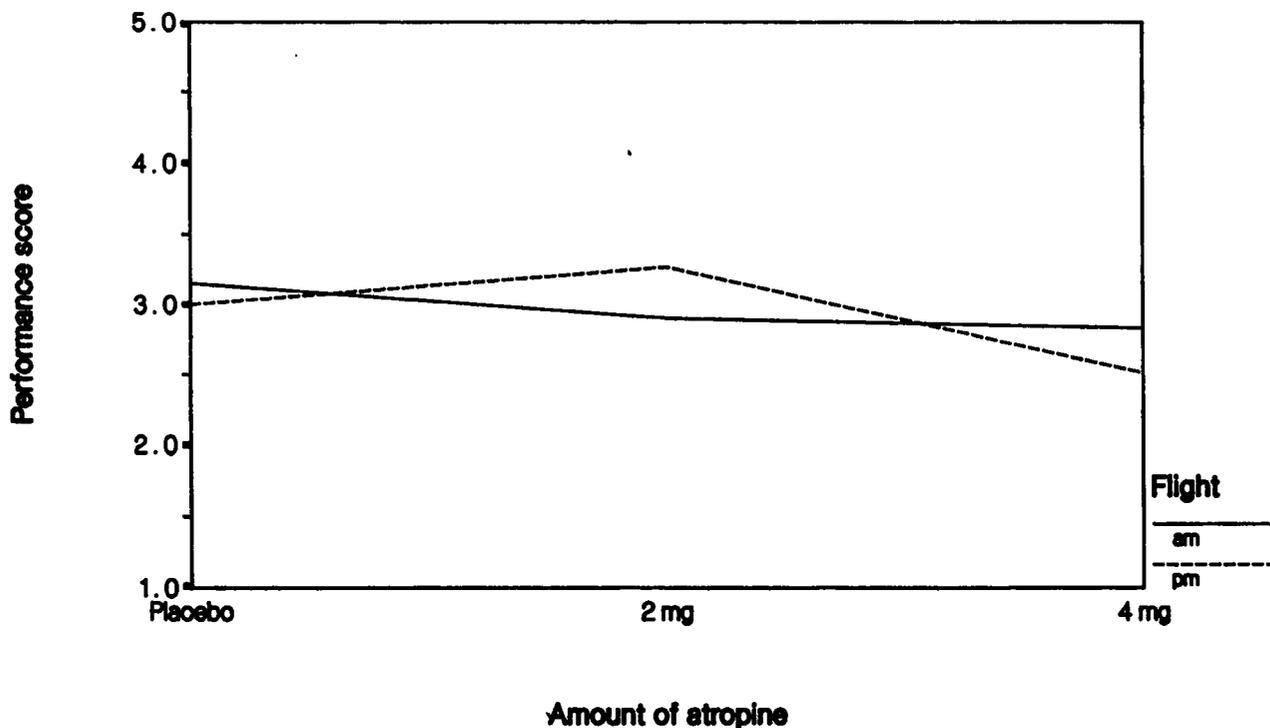


Figure 5. Dose X flight interaction for instrument takeoff during simulator flight.

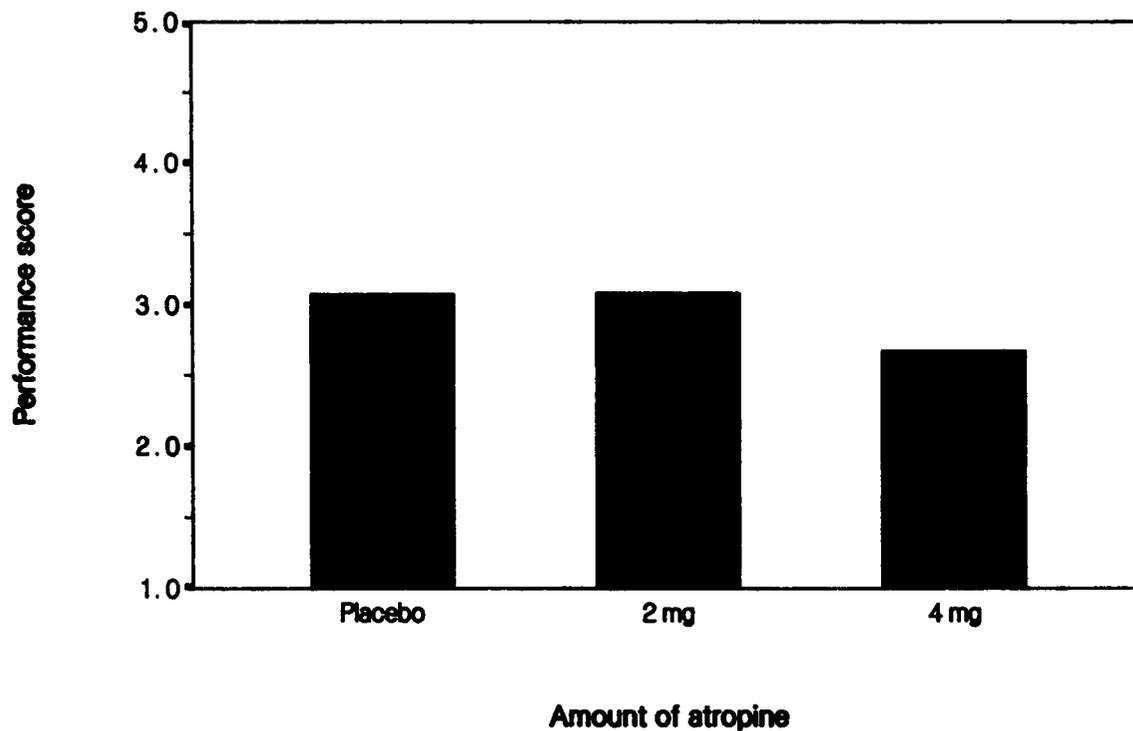


Figure 6. Dose main effect on instrument takeoff during simulator flight.

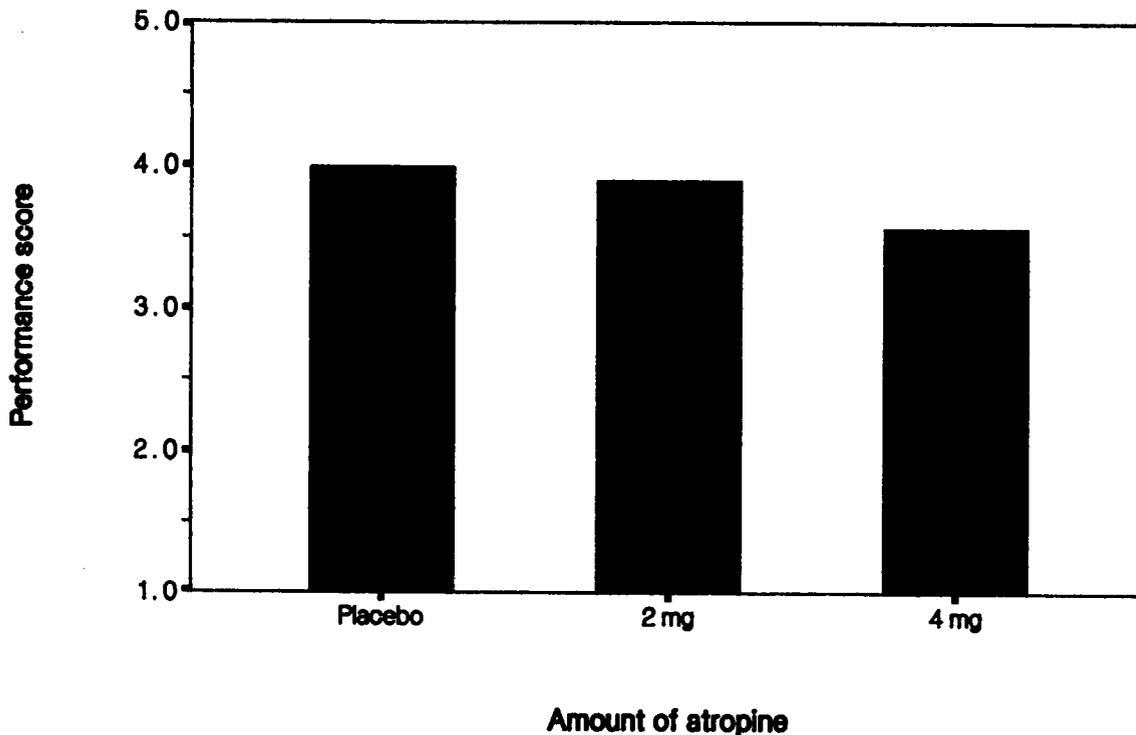


Figure 7. Dose main effect on level flight segment during simulator flight.

significantly lower in the 4 mg condition than in either of the other two dose conditions.

The analysis for the holding segment also indicated a dose main effect ($F(2,22)=8.68$, $p=0.0017$). The ratings (Figure 8) were lower in both the 2 mg condition ($F(1,11)=6.49$, $p=0.0271$) and the 4 mg condition ($F(1,11)=19.81$, $p=0.0010$) than they were in the placebo condition. The 2 mg and 4 mg conditions did not differ from each other.

The analysis of the IIS segment (Figure 9) also produced a dose main effect ($F(2,22)=3.51$, $p=0.0477$) which was due to lower ratings for the 4 mg flight than for the placebo flight ($F(1,11)=8.64$, $p=0.0135$). None of the other differences were significant.

Finally, analysis of the composite score (Figure 10) also revealed a significant dose main effect ($F(2,22)=20.22$, $p<0.0001$). This was accounted for by lower ratings for the 4 mg flight when compared to either the placebo ($F(1,11)=38.19$, $p=0.0001$) or the 2 mg flights ($F(1,11)=24.41$, $p=0.0004$). Ratings between the 2 mg and placebo flights did not differ.

It is noteworthy that the minimum rating required for the maintenance of ATM standards is a composite rating of 12. The

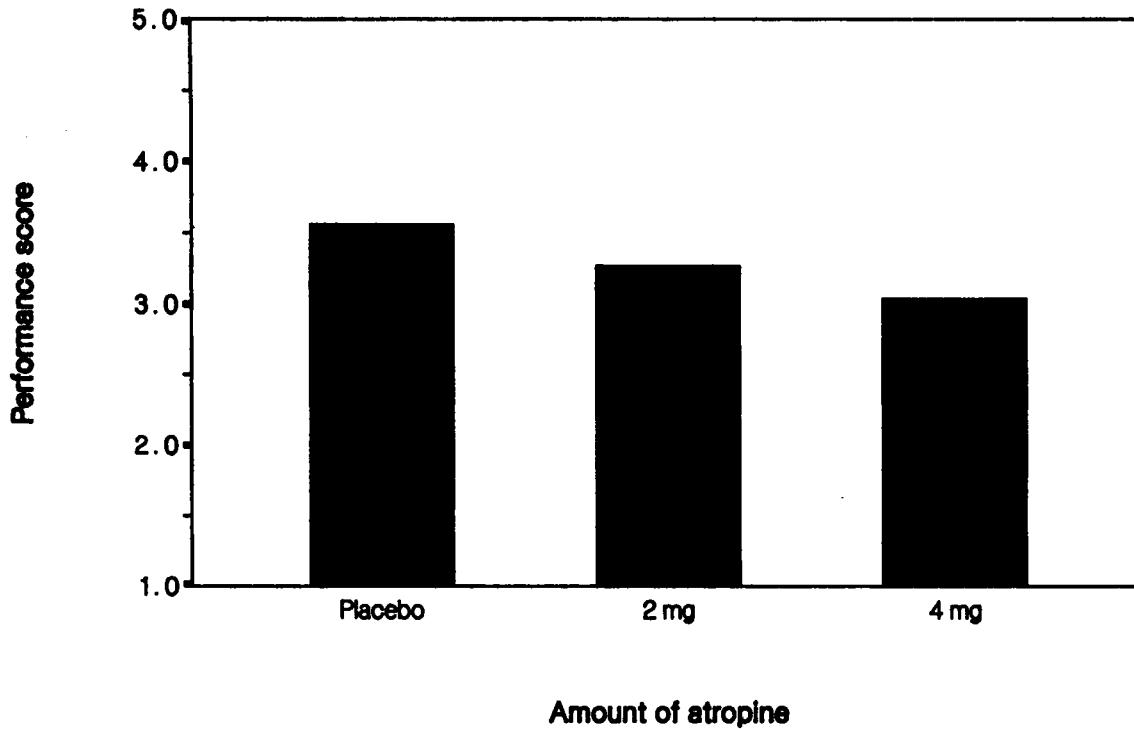


Figure 8. Dose main effect on holding segment during simulator flight.

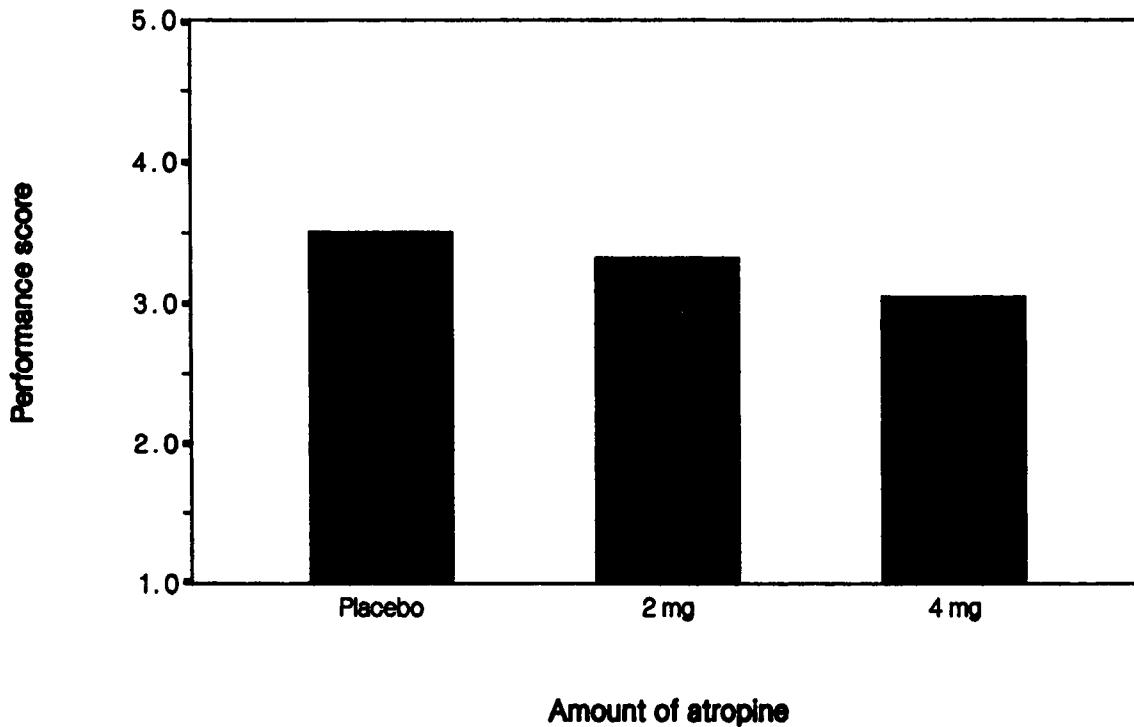


Figure 9. Dose main effect on ILS segment during simulator flight.

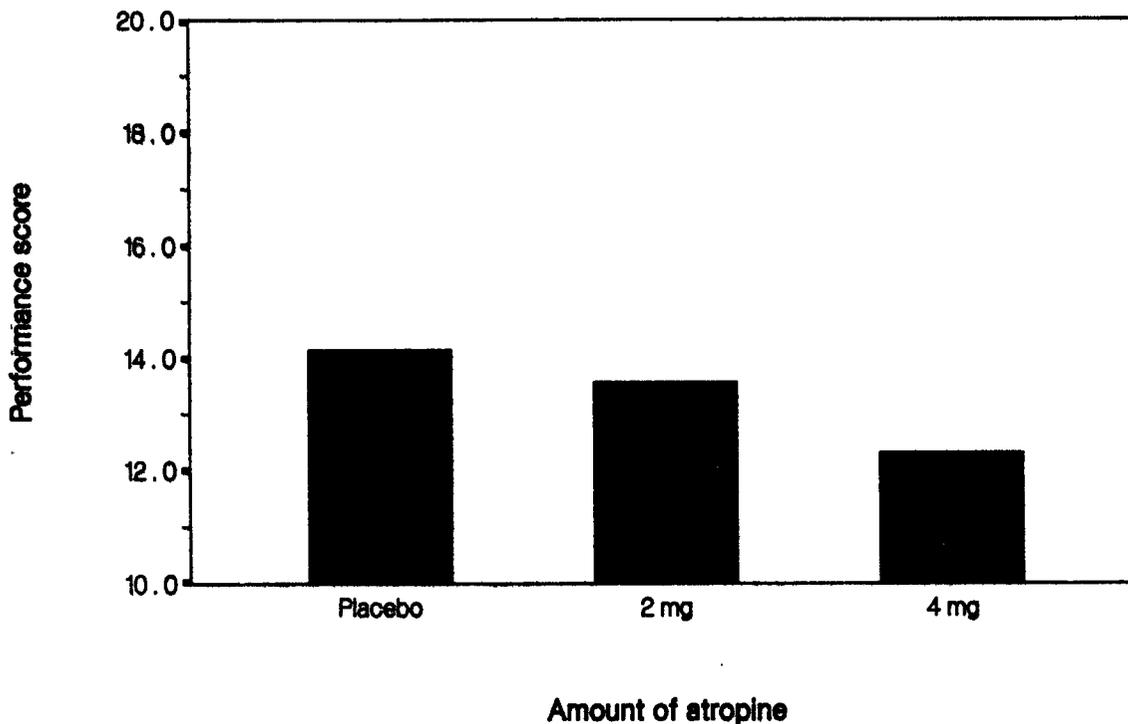


Figure 10. Dose main effect on composite score constructed from simulator flight.

mean composite scores for all subjects, collectively, in this investigation ranged from 14.2 for the placebo, to 12.6 for the 4 mg dose in the morning, and from 14.1 for placebo to 12.1 for 4 mg in the afternoon. Thus, the mean performance rating for the group--even with 4 mg of atropine--was always above minimum safe ATM standards.

However, an examination of individual performance ratings revealed performance of 5 of 12 aviators was rated below ATM standards (on mean composite subjective grades) under the 4 mg dose. One of these subjects fell below standards only on the afternoon of the 4 mg day and one fell below standards on the morning of the 2 mg day and on the afternoon of the 4 mg day. A third subject was rated below standards on the morning of the placebo dose and on both the morning and the afternoon of the 4 mg dose. The remaining two subjects were rated below ATM standards on every flight during the study. Another subject (not mentioned in the above group), while under the influence of 4 mg atropine, allowed the simulator to "crash" (both in the morning and in the evening). This pilot did not correct a slow and progressive loss of altitude during the execution of maneuvers (which were to be flown at 600 feet above ground level) and the simulator ultimately came into contact with the "ground."

Objective measures of flight performance

Once each subject completed all simulator flights, two different data files were created to describe the subject's performance in detail. One file contained a running record of digitized instrument readings and control movements (each channel was sampled at a preselected rate) followed by descriptive statistics (minimum, maximum, mean, and standard deviation) for each maneuver. The second file contained the root mean square (RMS) errors⁴ and the performance scores of interest for each maneuver. See Table 8 for a listing of the objectively rated maneuvers and the respective variables.

Table 8.

Maneuvers and variables objectively examined

Maneuver	Variables
HAAT	Heading, altitude, airspeed, climb rate
Climbing turn	Airspeed, climb rate, turn rate
Descending turn	Airspeed, climb rate, turn rate
Level flight	Heading, altitude, airspeed, climb rate
ILS Approach	Airspeed, localizer, glideslope

Performance scores were expressed as percentages which ranged from 100 to 0 percent. The scores were calculated by first determining how many total samples were collected on each variable (i.e., airspeed, altitude, climb rate, etc.) and then categorizing each sample into one of 6 bins (100, 80, 60, 40, 20, or 0 percent) depending upon how far that sample deviated from a predetermined standard (Table 9). Thus, at the conclusion of this first step, each bin contained one integer value which represented the number of samples classified into that particular bin. The number of samples in each bin was then multiplied by the weighting factor

⁴The 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 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 RMS error is calculated using differences from an ideal value rather than from a mean.

for the respective bin (100, 80, 60, 40, 20, or 0) and 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 variable.

During an initial overview of the scoring procedures, bandwidths were established to the tolerances established by Army Training Circular (TC) 1-211, the Aircrew Training Manual Utility Helicopter, UH-1. However, the scores obtained via this scoring procedure did not offer the precision necessary to adequately distinguish the performance changes of interest because the bandwidths were too lenient. For example, scores obtained for the level flight maneuver showed virtually all of the subject pilots were within training standards for heading (+/-10 degrees), altitude (+/-100 feet), and airspeed (+/-10 knots) almost all of the time. Thus, the bandwidths required readjustments which, upon completion, narrowed each scoring band substantially. With these more rigorous scoring criteria, the ability to discern the performance differences of interest was improved greatly.

All of the RMS scores were subjected to a natural log transformation. Performance scores, expressed in percentages, were converted to proportions and then transformed using the $2 \cdot \arcsin(\sqrt{x})$ conversion (Winer, 1971). Following these transformations, regression analyses were performed to determine whether or not a linear relationship existed between each of the dependent measures and the session number (or elapsed number of flights). The presence of such a relationship would suggest the need to correct the data set in order to remove a confounding learning effect. Each dependent measure for which there was a significant linear relationship with session was adjusted by subtracting the portion of the score which was attributable to learning (as indicated by the regression). Of the 98 dependent measures, 39 showed a significant learning or skill development trend with session and were corrected accordingly.

Performance scores and log RMS errors then were subjected to repeated measures analyses of variance to test for significant effects ($p < 0.05$) attributable to dose (placebo, 2 mg, or 4 mg) and/or flight (am or pm). A significant dose x flight interaction was observed on turn rate score in the descending turn ($F(2,22) = 3.76, p = 0.0393$); but, analysis of simple effects (Figure 11) revealed no significant differences. However, examination of Figure 11 suggests the interaction was due largely to the difference in performance scores for the morning and afternoon flights for the placebo and 4 mg conditions. Morning session scores tended to be higher than afternoon session scores under placebo, while the opposite trend was observed for the 4 mg condition. Differences due to dose or flight alone were not significant.

Table 9.
Scoring error bands

<u>Variable</u>	<u>Band limits</u>					<u>Units</u>	
	<u>Score</u>	100%	80%	60%	40%	20%	0%
Heading	0- 0.500	0.500- 1.00	1.00- 2.0	2.0- 4.0	4.0- 8.0	> 8.0	Deg
Altitude	0- 5.000	5.000-10.00	10.00- 20.0	20.0- 40.0	40.0- 80.0	> 80.0	Feet
Airspeed	0- 0.500	0.500- 1.00	1.00- 2.0	2.0- 4.0	4.0- 8.0	> 8.0	Knots
Climb rate	0-25.000	25.000-50.00	50.00-100.0	100.0-200.0	200.0-400.0	>400.0	Ft/min
Turn rate	0- 0.250	0.250- 0.50	0.50- 1.0	1.0- 2.0	2.0- 4.0	> 4.0	Deg/sec
Localizer	0- 0.125	0.125- 0.25	0.25- 0.5	0.5- 1.0	1.0- 2.0	> 2.0	Dots ⁶
Glideslope	0- 0.125	0.125- 0.25	0.25- 0.5	0.5- 1.0	1.0- 2.0	> 2.0	Dots

⁶"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 4 dots, represents a flight path above or below a 0.7 degree envelope. Fractional readings are common. The significance of any given deflection increases in severity with proximity to the runway.

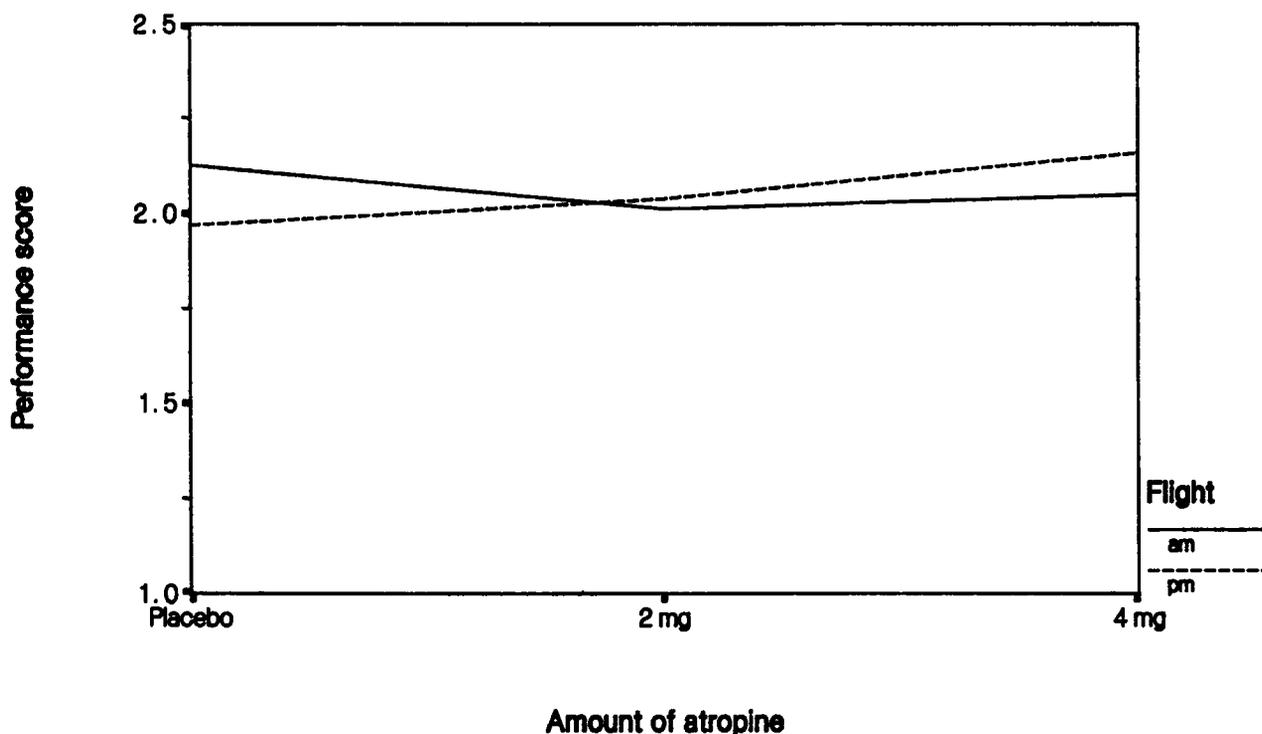


Figure 11. Dose X flight interaction for descending turn during simulator flight.

In the HAAT maneuver, there was a significant dose x flight interaction on both airspeed variables, RMS error ($F(2,22)=5.17$, $p=0.0144$) and performance score ($F(2,22)=5.01$, $p=0.0161$). Analysis of simple effects on the airspeed RMS error (Figure 12) showed a statistically significant increase in error from morning to evening under placebo ($F(1,11)=5.54$, $p=0.0383$), but not under 2 mg or 4 mg. Simple effects on the airspeed performance scores (Figure 13) indicated none of the differences between flights were statistically significant at any of the three dosage levels.

Contrasts between the dose levels were examined to identify the source of the main effects (Table 10). Overall, performance on all measures for which there was a dose effect was degraded significantly between placebo and 4 mg of atropine, seven of the measures showed a significant decrement between 2 mg and 4 mg atropine, and only four of the measures revealed significant performance decrements between placebo and 2 mg atropine.

Two measures of HAAT heading showed a dose effect (Figure 14): Heading RMS error ($F(2,22)=7.42$, $p=0.0034$) and the computer-generated score ($F(2,22)=3.86$, $p=0.0366$). In both cases, performance was poorer at 4 mg than at either 2 mg or placebo, but was not different between placebo and 2 mg.

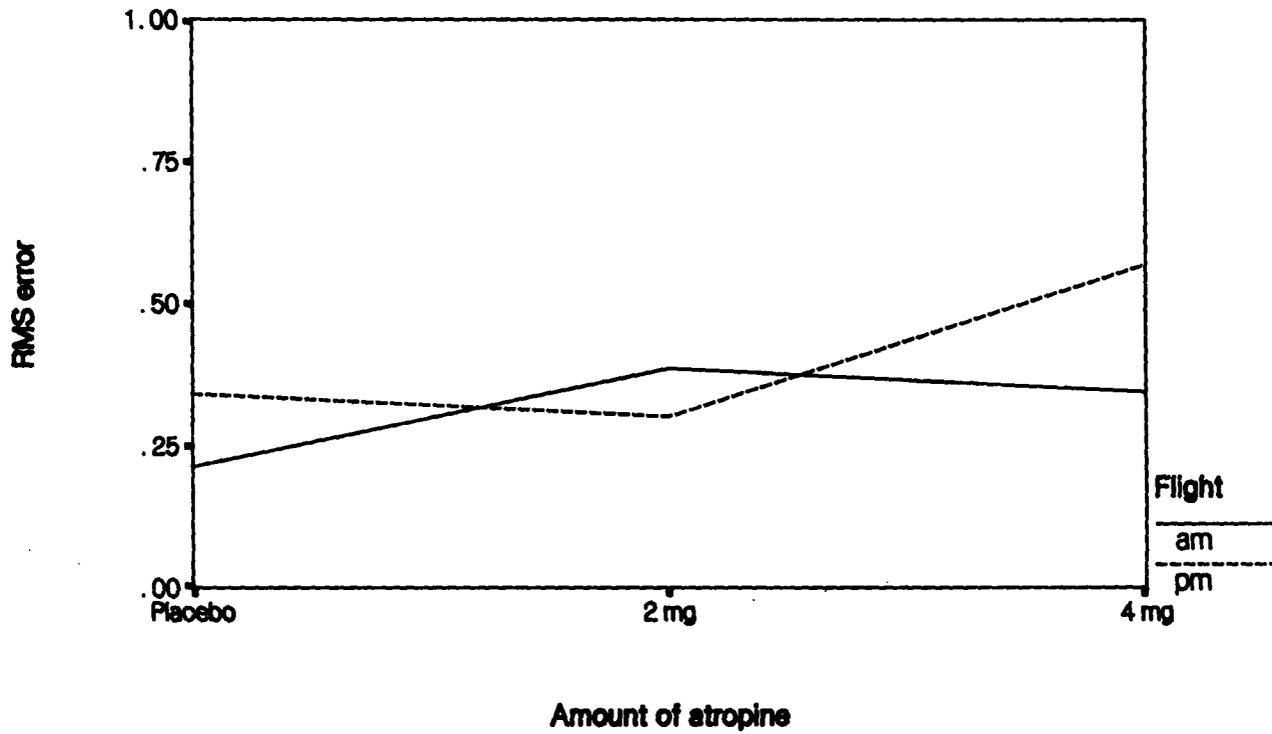


Figure 12. Dose X flight interaction for airspeed RMS error during HAAT maneuvers in simulator.

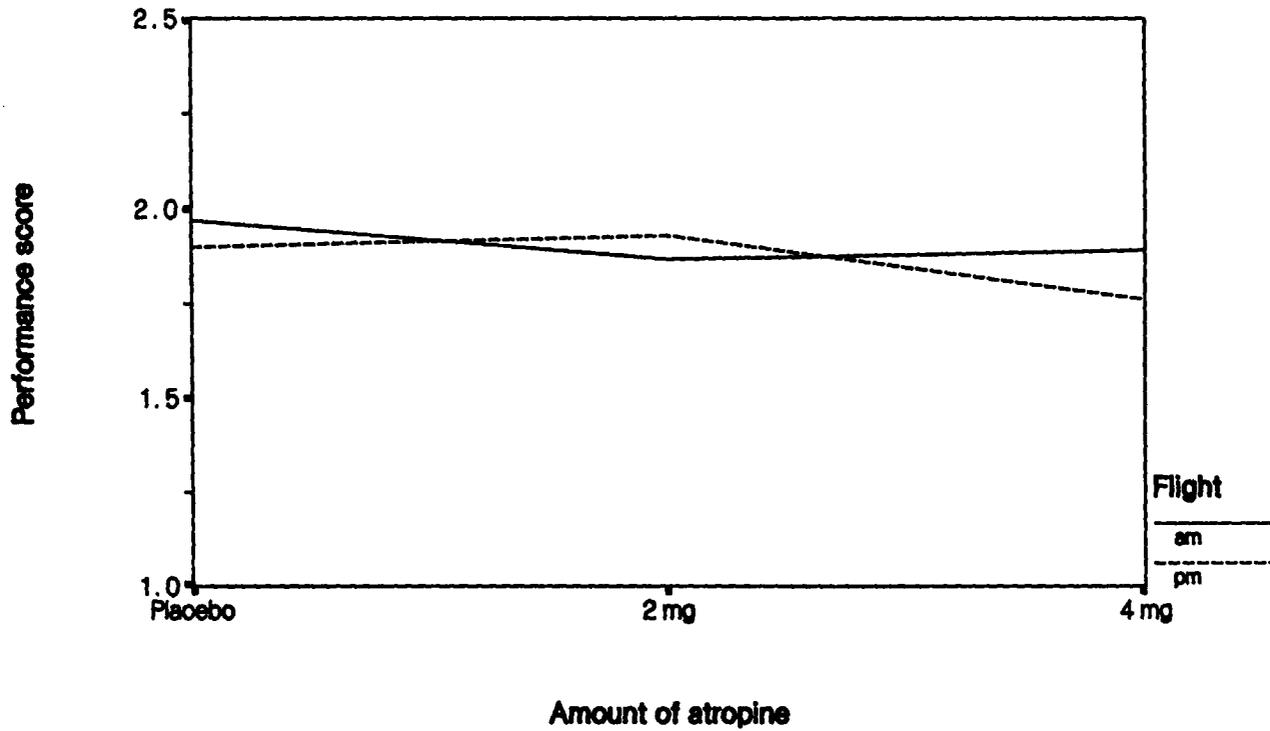


Figure 13. Dose X flight interaction for airspeed performance scores during HAAT maneuvers in simulator.

Table 10.

Results of dose main effect contrasts for simulator flight objective measures

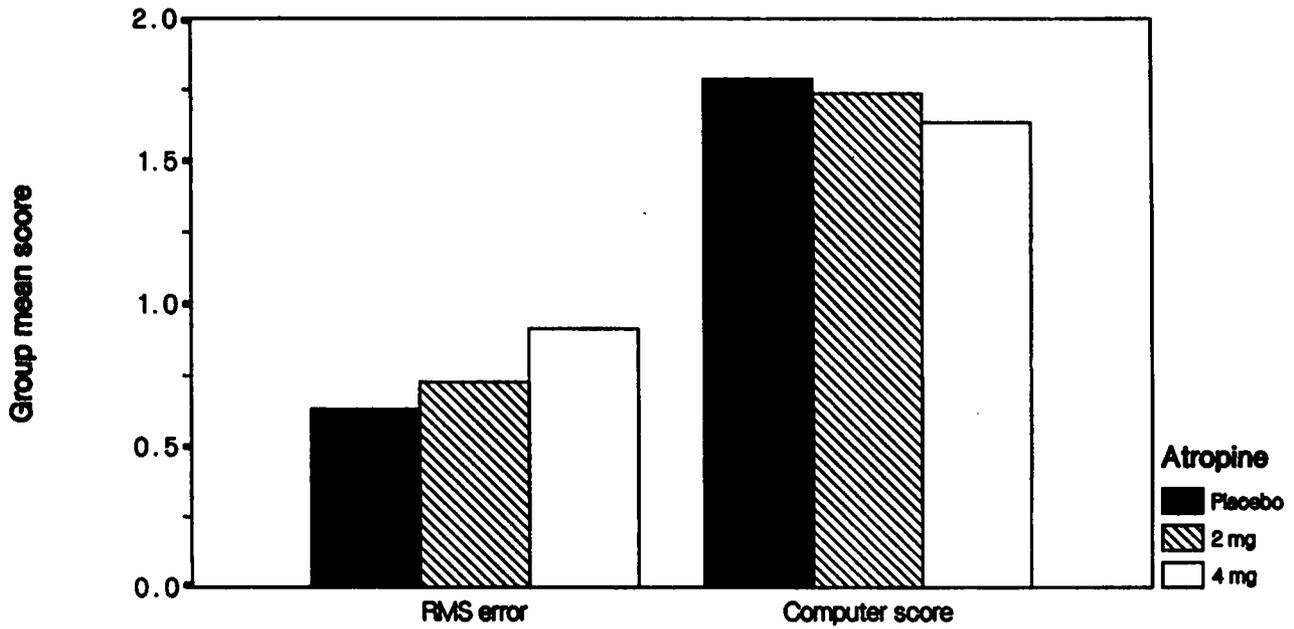
	0mg/2mg	0mg/4mg	2mg/4mg
<u>Log RMS errors</u>			
SL heading	0.0129	0.0024	ns
SL altitude	ns	0.0010	0.0463
SL airspeed	ns	0.0003	0.0094
SL climb rate	0.0238	0.0003	ns
CT climb rate	ns	0.0071	0.0317
HAAT heading	ns	0.0056	0.0090
<u>Computer error band scores</u>			
SL heading	0.0033	0.0043	ns
SL altitude	ns	0.0138	0.0210
SL airspeed	ns	0.0006	0.0011
SL climb rate	0.0265	0.0001	ns
HAAT heading	ns	0.0223	0.0284

Note: ns = $p > 0.05$

In the climbing turn maneuver, only one variable, vertical speed RMS error (Figure 15), revealed a dose effect ($F(2,22)=4.49$, $p=0.0232$). Here again, performance was poorer at 4 mg than at either 2 mg or placebo.

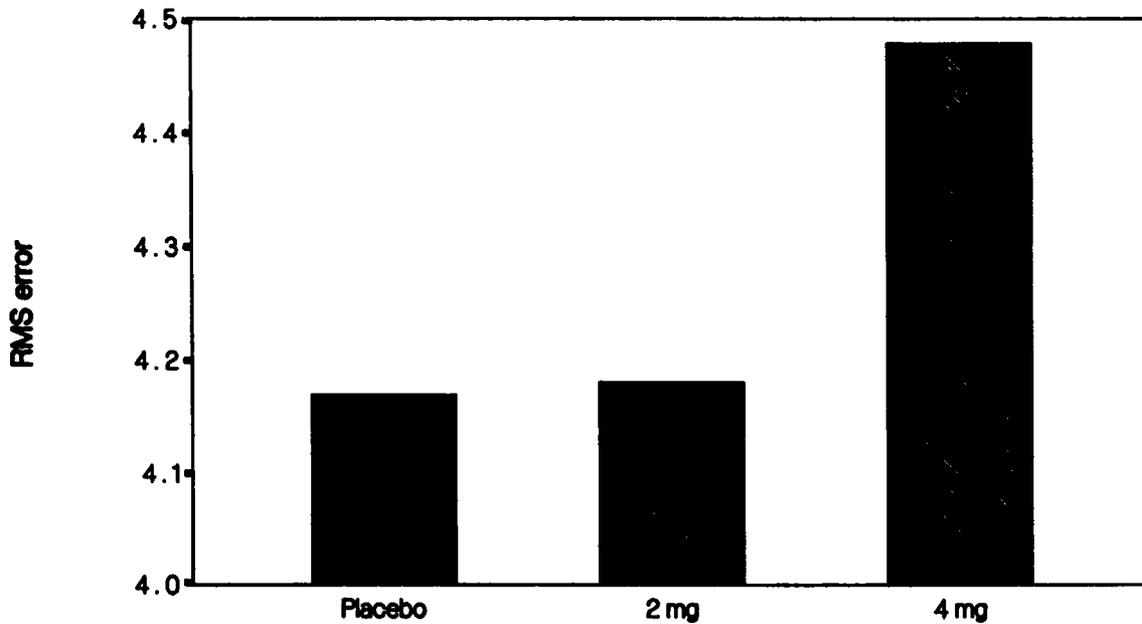
In the straight and level maneuver, all RMS error variables (Figure 16) were affected significantly by dose: heading ($F(1.28,14.13)=7.47$, $p=0.0177$); altitude ($F(2,22)=8.17$, $p=0.0022$); airspeed ($F(2,22)=13.30$, $p=0.0002$); vertical speed ($F(2,22)=10.60$, $p=0.0006$). Changes in heading and vertical speed were attributable to differences between the placebo condition and both the 2 mg and the 4 mg conditions. Changes in altitude and airspeed occurred with the 4 mg dose as compared to both the 2 mg dose and the placebo (see Table 10).

Performance score variables (Figure 17) also were affected: heading ($F(1.28,14.09)=7.25$, $p=0.0129$); altitude ($F(2,22)=4.86$, $p=0.0179$); airspeed ($F(2,22)=16.43$, $p<0.0001$); and vertical speed ($F(2,22)=13.00$, $p=0.0002$). The pattern for contrasts was the same as for RMS errors (see Table 10, above).



Heading

Figure 14. Dose main effect on heading and computer score during HAAT maneuvers in simulator.



Amount of atropine

Figure 15. Dose main effect on vertical speed RMS error during climbing turn in simulator flight.

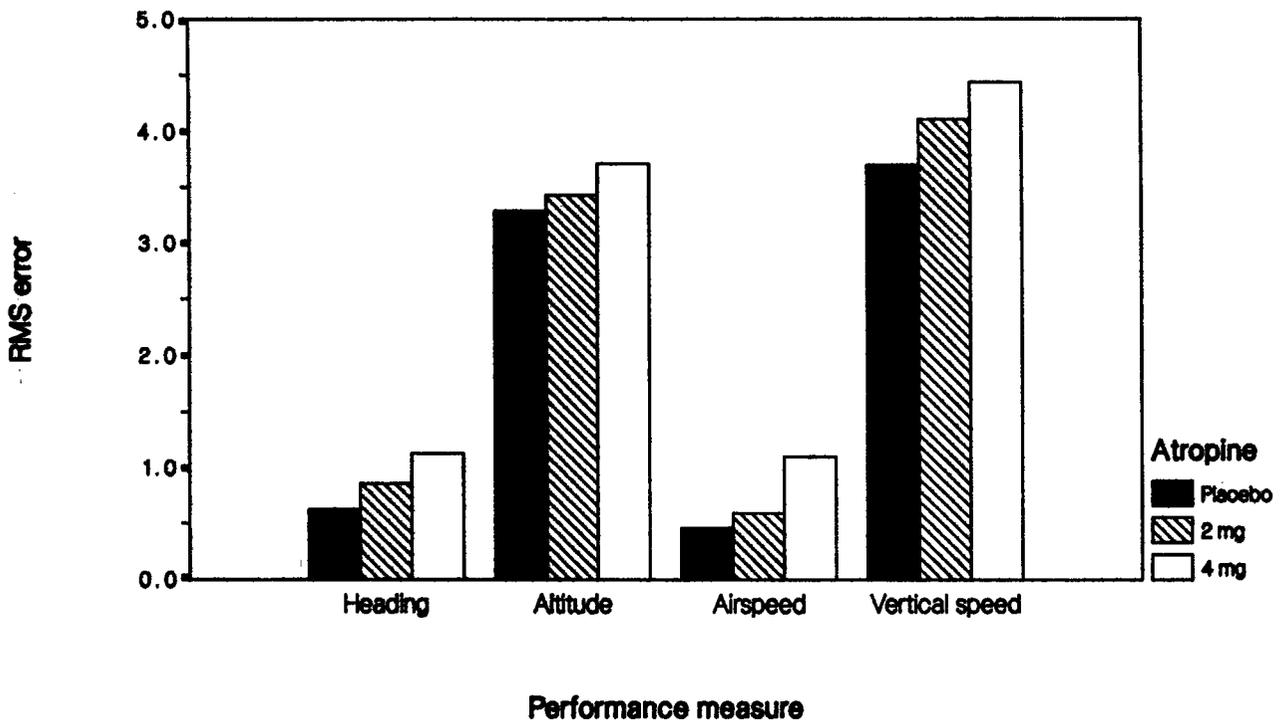


Figure 16. Dose main effect on heading, altitude, airspeed, and vertical speed RMS error during straight-and-level segment of simulator flight.

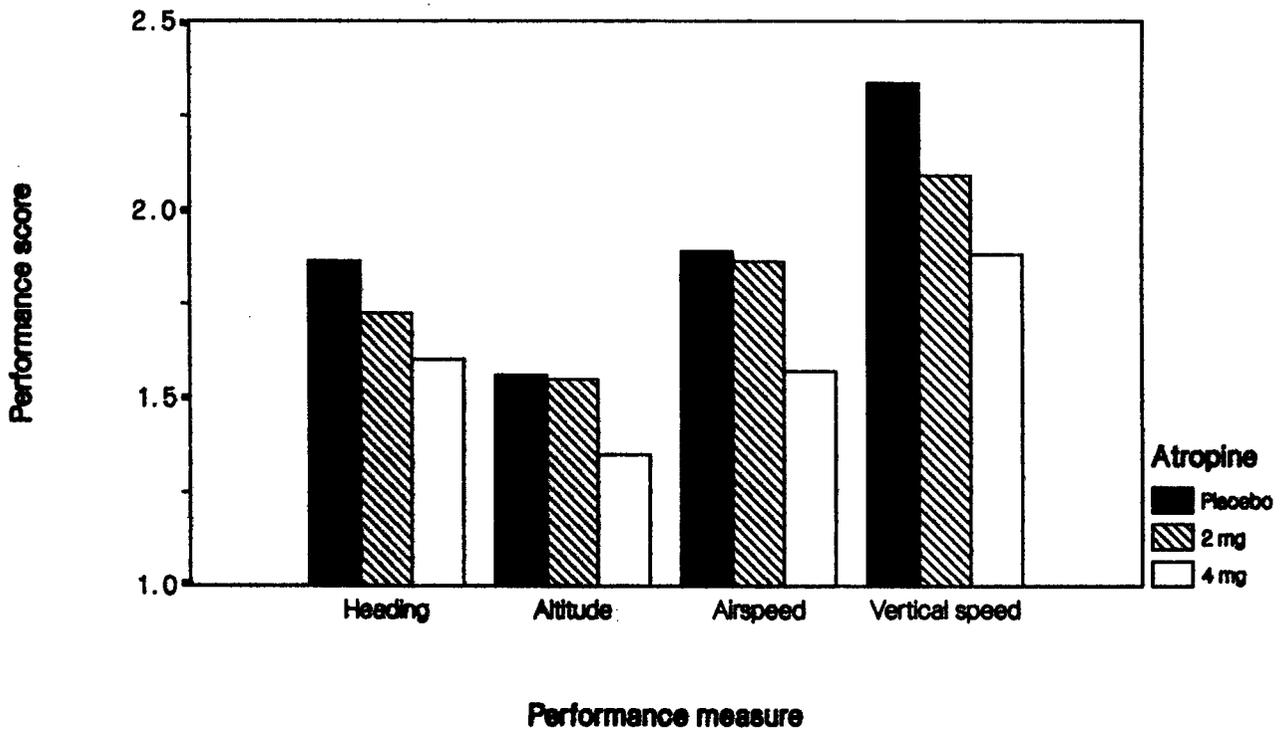


Figure 17. Dose main effect on heading, altitude, airspeed, and vertical speed performance score during straight-and-level segment of simulator flight

A main effect due to flight (Figure 18) was observed only in the straight and level maneuver and only for heading RMS error ($F(1,11)=10.50$, $p=0.0079$). An examination of the group means revealed a performance degradation in the afternoon flight relative to the morning flight.

There were no significant effects in the ILS approach, although two of the variables, the localizer score ($p=0.0666$) and localizer RMS error ($p=0.0541$), approached significance for dose.

With respect to the nine HAAT maneuvers, a significant dose X HAAT interaction was found for the airspeed RMS error ($F(16,176)=1.72$, $p=0.0471$), but not for any other measures.

Analysis of simple effects (Figure 19) showed the interaction was due to a significant effect for dose at HAAT 7 ($F(2,22)=6.19$, $p=0.0074$). One of the subsequent contrasts, comparing the 2 mg to the 4 mg dose at HAAT 7, revealed a significant effect ($F(1,11)=14.67$, $p=0.0084$); but, the differences between placebo and 4 mg and between placebo and 2 mg were not significant. Examination of HAAT 7 cell means indicated the RMS error was greatest under the 4 mg condition and least under the 2 mg condition.

Finally, the analysis of variance on the nine HAAT maneuvers further revealed a HAAT main effect for heading score ($F(8,88)=3.54$, $p=0.0014$); altitude score ($F(8,88)=3.64$, $p=0.0010$); heading RMS error ($F(8,88)=2.36$, $p=0.0237$); altitude RMS error ($F(8,88)=3.53$, $p=0.0014$); and vertical speed RMS error ($F(8,88)=2.56$, $p=0.0147$). However, these differences were of little interest since they reflect only time-related or task-related changes which did not interact systematically with either dose or flight.

Contrast sensitivity function

The contrast sensitivity findings for all conditions are presented graphically in Figure 20. The three panels on the left depict the results obtained under normal laboratory illumination, while those on the right were obtained with the glare source turned on. The uppermost panels summarize the placebo results; the middle panels the 2 mg results; and the bottom panels the 4 mg results.

A repeated measures ANOVA was performed on the log threshold contrast measures obtained on the placebo days. There were no statistically significant differences in thresholds obtained prior to saline injection and those obtained approximately 2 and 7 hours later, indicating contrast thresholds in the absence of drug were stable over the test day, there being no consistent diurnal, practice, or fatigue effect. Because of this stability, all

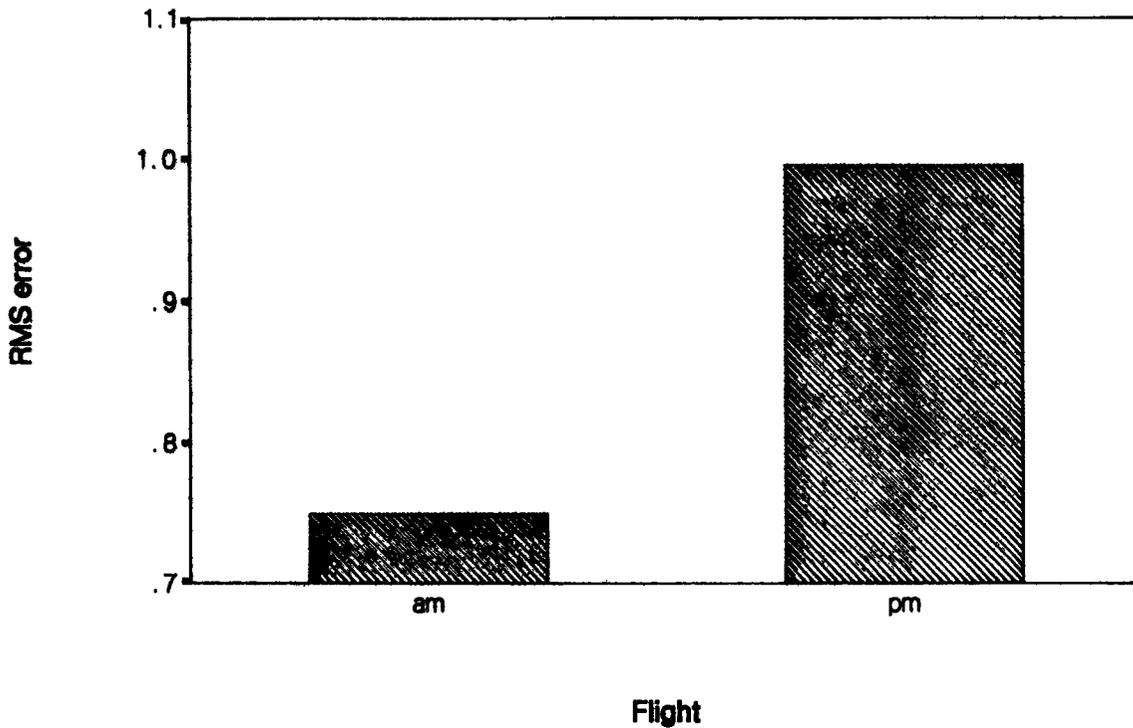


Figure 18. Flight main effect on heading RMS error during straight-and-level segment of simulator flight.

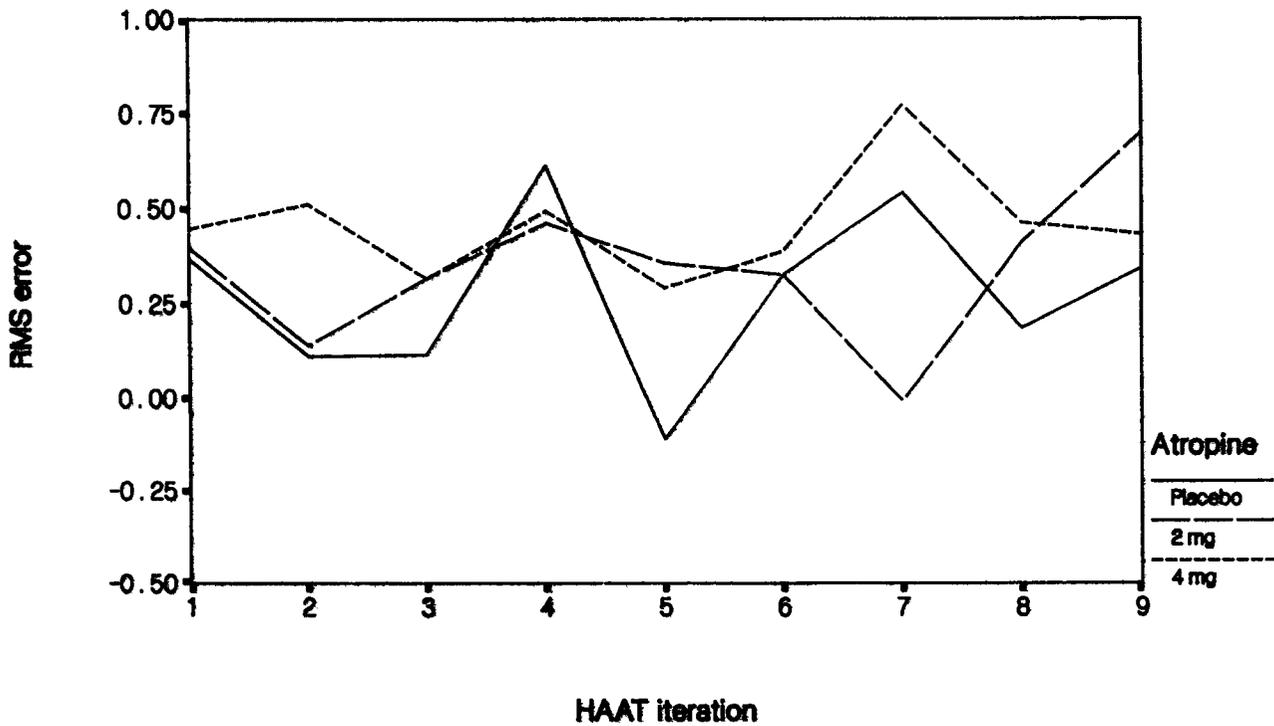


Figure 19. Dose X HAAT iteration interaction for simulator flight.

Visual contrast sensitivity

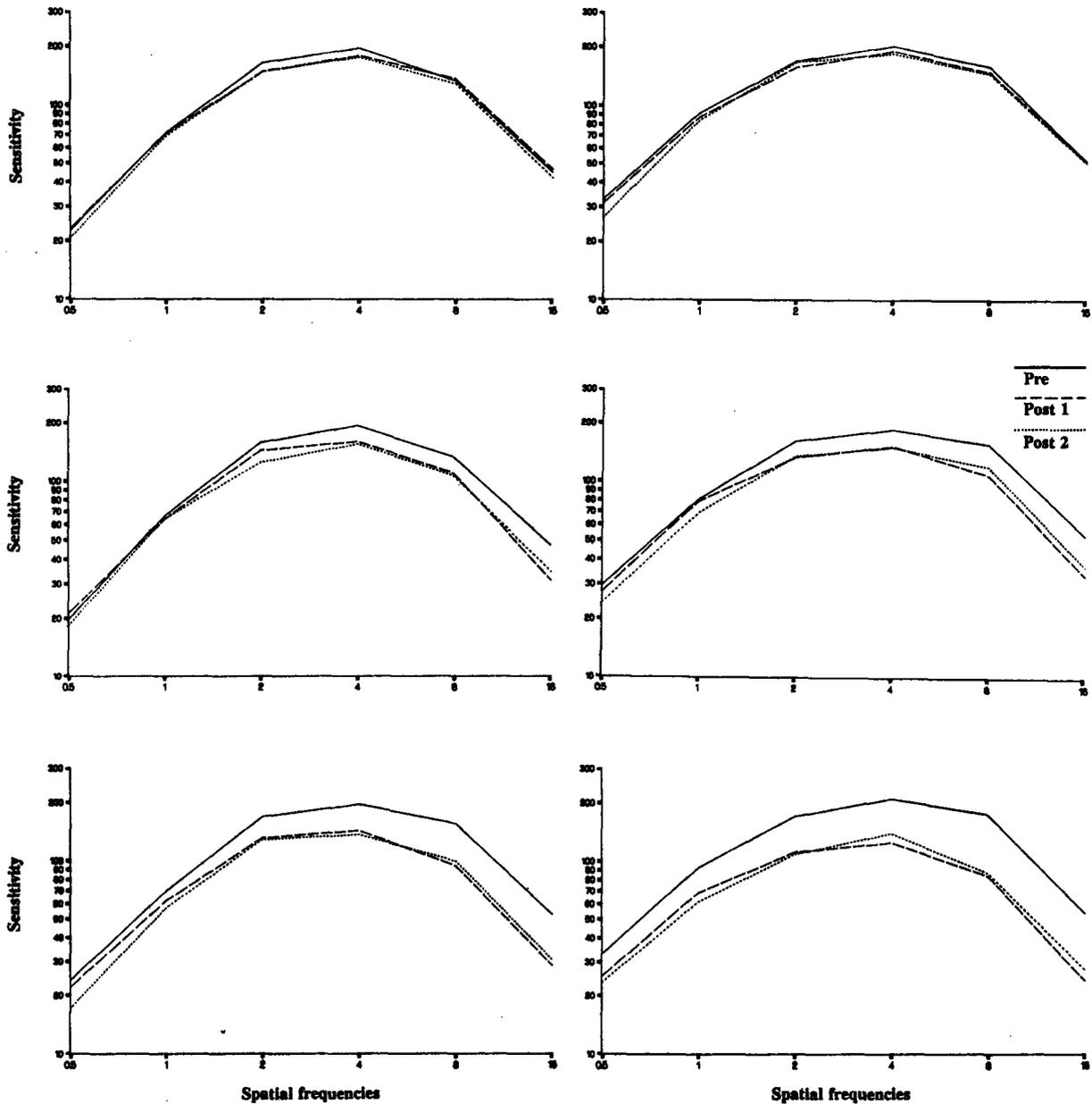


Figure 20. Dose (vertical) X glare (horizontal) interaction for contrast sensitivity function.

atropine effects were evaluated against their same-day preinjection baseline thresholds. There was, as would be expected, a highly significant spatial frequency effect ($F(5,55)=124.54$, $p<0.0001$) and an unexpected superior mean contrast sensitivity of 93.1 in the presence of glare versus 79.8 under normal illumination. The interaction of glare by spatial frequency (Figure 21, "0 mg") was also significant ($F(5,55)=6.05$, $p<0.0002$) reflecting the greater difference in sensitivity at the extreme spatial frequencies than for those in the middle.

In comparison to the CSFs obtained with saline injection, those obtained when 2 mg or 4 mg of atropine were administered were significantly reduced relative to the preinjection baseline CSFs, especially for the spatial frequencies 2 cpd and above. A repeated measures ANOVA of the 2 mg log thresholds yielded a highly significant session by spatial frequency interaction ($F(10,110)=10.27$, $p<0.0001$), reflecting the virtual absence of an atropine-related loss in contrast sensitivity for the spatial frequencies below 2 cpd and moderate losses for the spatial frequencies above 2 cpd. Also, a highly significant session effect ($F(2,22)=22.38$, $p<0.0001$) showed visual losses in the afternoon and evening (2 and 7 hours postinjection) relative to morning (preinjection). Mean preinjection contrast sensitivity was 85.5, while means for afternoon and evening were 71.3 and 69.6, respectively, consistent with the known long lasting effects of atropine in the visual system (Gilman, Goodman, and Gilman, 1980). As with the placebo, contrast sensitivity at 2 mg was slightly but significantly better in the presence of glare ($F(1,11)=16.75$, $p<0.0018$), notably at the extreme spatial frequencies (the interaction of glare by spatial frequency was ($F(5,55)=14.90$, $p<0.0001$)). However, the loss in sensitivity due to atropine was no greater in the presence of glare than under normal illumination.

The results for the 4 mg conditions were qualitatively similar to those described above for the 2 mg conditions, the magnitude of the atropine effects being, however, considerably larger. Again, the visual losses obtained 2 and 7 hours after the atropine administration were nearly identical (mean preinjection contrast sensitivity was 93.6, while means for afternoon and evening were 62.1 and 61.0, respectively). A repeated measures ANOVA of the 4 mg log thresholds yielded a highly significant session effect ($F(2,22)=37.10$, $p<0.0001$), as well as a significant session by spatial frequency interaction ($F(10,110)=7.82$, $p<0.0001$), again reflecting the larger atropine effect at the higher spatial frequencies. In comparison to the results obtained with 0 and 2 mg doses, the mean contrast sensitivity was equivalent under the two illumination conditions, 69.9 in the absence of glare and 71.7 in its presence, and the effect of glare per se was not significant. The interaction of glare by spatial frequency was significant ($F(5,55)=15.90$, $p<0.0001$). As can be seen in Figure 21, 4 mg performance was better with glare below 2 cpd, while it was

Visual contrast sensitivity

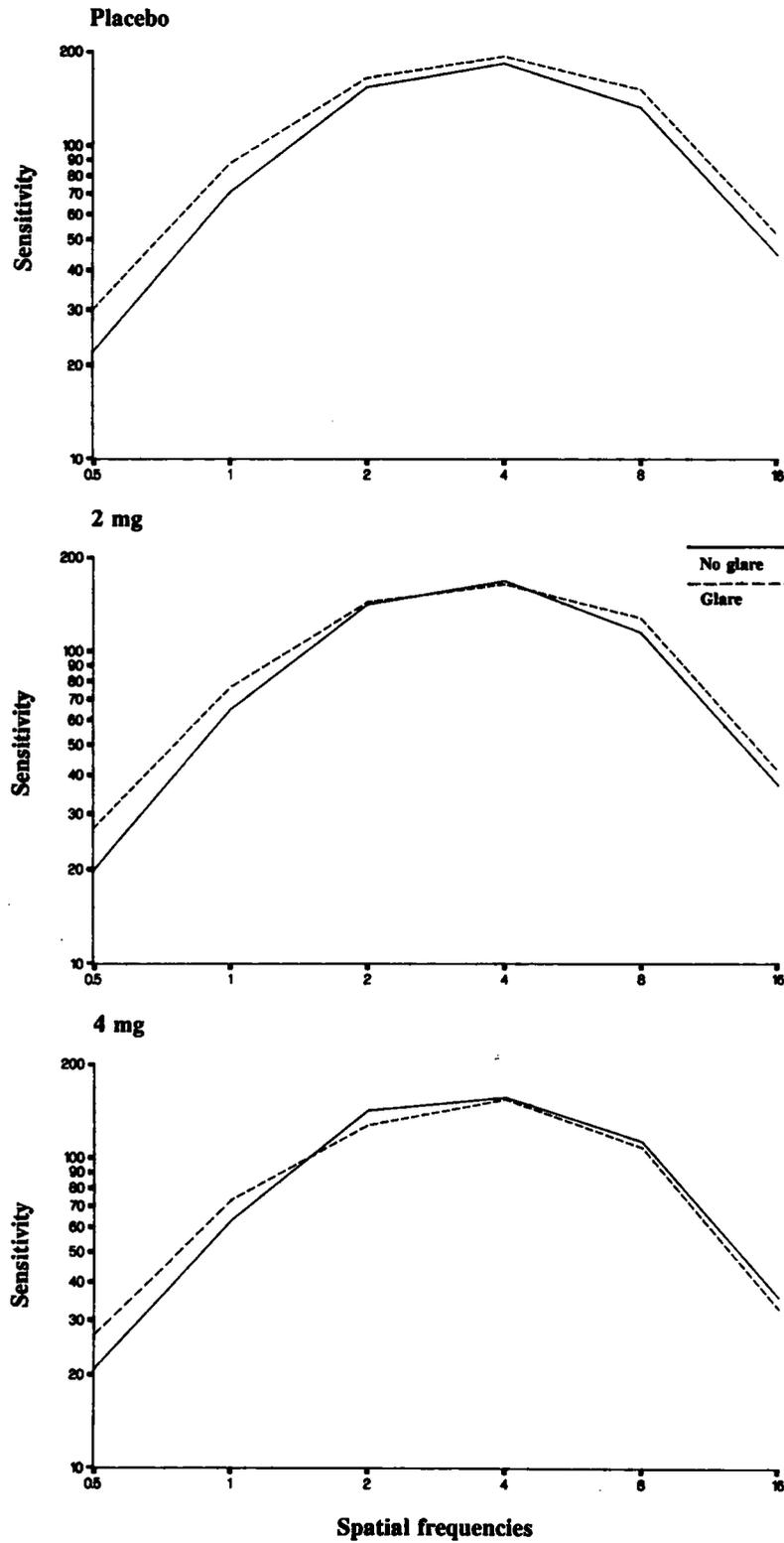


Figure 21. Dose main effect on contrast sensitivity function.

better under normal illumination at 2 epd and above. In contrast to the 2 mg results, the loss in sensitivity due to atropine was greater in the presence of glare for all spatial frequencies than under normal illuminations; for the session by glare interaction, $F(2,22)=8.94$, $p=0.0014$.

Performance assessment battery

Each of the five (discounting the mood-activation scale, which was not analyzed for this report) subtests of the WRAIR PAB generated 18 dependent measures. Some of these measures convey redundant information, while others are of limited usefulness for statistical analysis. For subsequent analyses, six variables from each subtest were deemed useful for examining the effects of atropine on cognitive performance: 1) the number of items attempted, 2) the number correct, 3) the mean reaction time (RT) for correct responses, and three derived measures: 4) the percent correct, 5) speed (total number of responses/min), and 6) throughput (correct responses/min).

These six variables were examined for practice effects on each of the five subtests using a repeated-measures ANOVA with day-of-test as the within subjects factor. This analysis was performed only on morning scores to determine how performance without drugs changed over time. Results revealed a significant change in performance across morning sessions for a majority of the measures.

To correct for these potentially confounding temporal changes, analysis of covariance (ANCOVA) was employed with each day's morning session score serving as the covariate for the same day's noon and evening session scores. These analyses involved a 3 X 2 factorial treatment structure with repeated measures on both factors; dose (placebo, 2, and 4 mg) and session (noon and evening). The analysis for the percent correct measure used the same strategy as above; however, before analyses were carried out on any of the percent correct measures, they were first converted to proportions and then transformed using the $2 \cdot \arcsin(\sqrt{x})$ transformation (Winer, 1971). The transformed data were expressed as an angle measured in radians, and assumed values between 0.0633 and 3.0783 for proportions ranging between 0.001 and 0.999 (Neter, Wasserman, and Kutner, 1985). The p-values for all contrasts were corrected using the Bonferroni procedure.

The analyses for the six-letter search task revealed no significant interactions between session and dose. Significant dose main effects were seen for the number attempted ($F(2,21)=3.67$, $p=.0430$), the number correct ($F(2,21)=8.64$, $p=.0018$), and percent correct ($F(2,21)=14.53$, $p=.0001$). Contrasts for the dose main effect on number attempted (Figure 22) showed subjects attempted significantly fewer problems after 2 mg of atropine than after

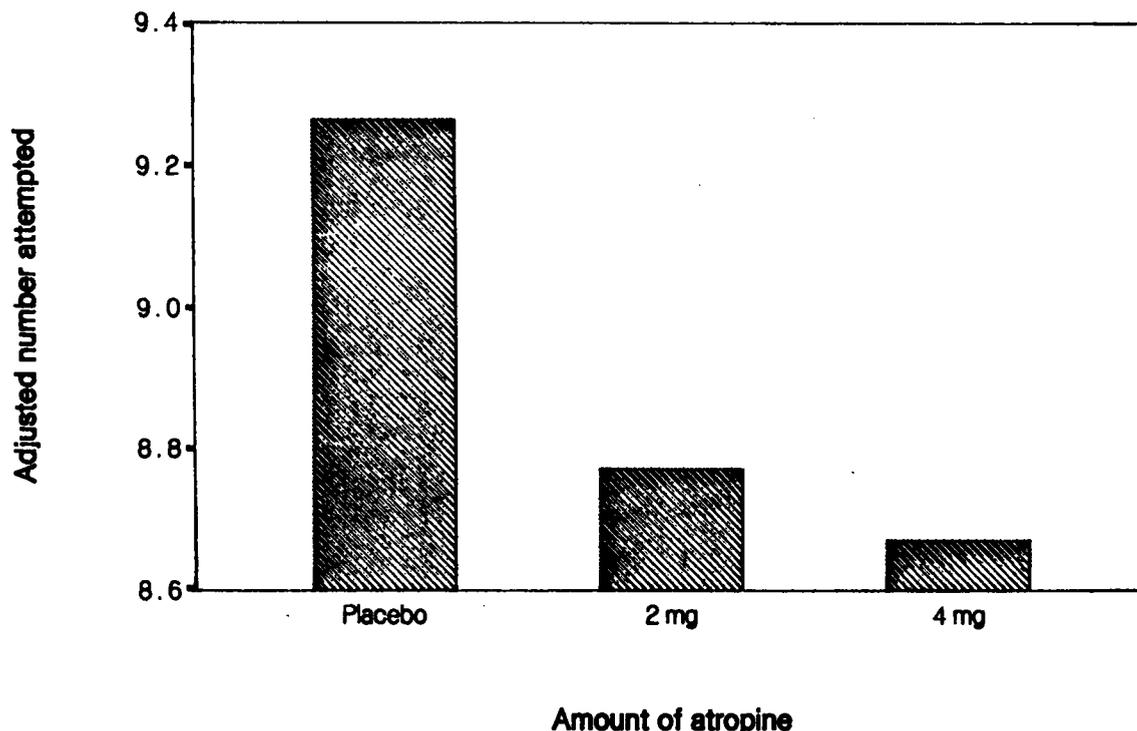


Figure 22. Dose main effect on number attempted during the six-letter search task of the PAB.

placebo ($F(1,10)=15.88$, $p=.0078$). Under the 4 mg condition, the number attempted was reduced by a similar amount; however, the contrast comparing placebo to 4 mg was not significant due to the greater variability associated with the 4 mg condition. Contrasts for the dose main effect on number correct (Figure 23) revealed a significant reduction in performance after 4 mg of atropine compared to placebo ($F(1,10)=15.10$, $p=.0090$), but not compared to 2 mg of atropine. The contrasts for the dose effect on percent correct (Figure 24) revealed a decrease for the 4 mg condition compared to both the placebo condition ($F(1,10)=16.89$, $p=0.0063$) and the 2 mg condition ($F(1,10)=18.85$, $p=0.0045$).

There was a significant session main effect for mean RT for correct responses ($F(1,11)=5.77$, $p=0.0351$). The session effect (Figure 25) resulted from a slight decrease in mean RT for correct responses from noon to evening. For the speed measure, the session main effect (Figure 26) also was significant ($F(1,11)=10.15$, $p=0.0087$), indicating speed increased during the evening session compared to the noon session. Analysis of the throughput measure revealed no effects.

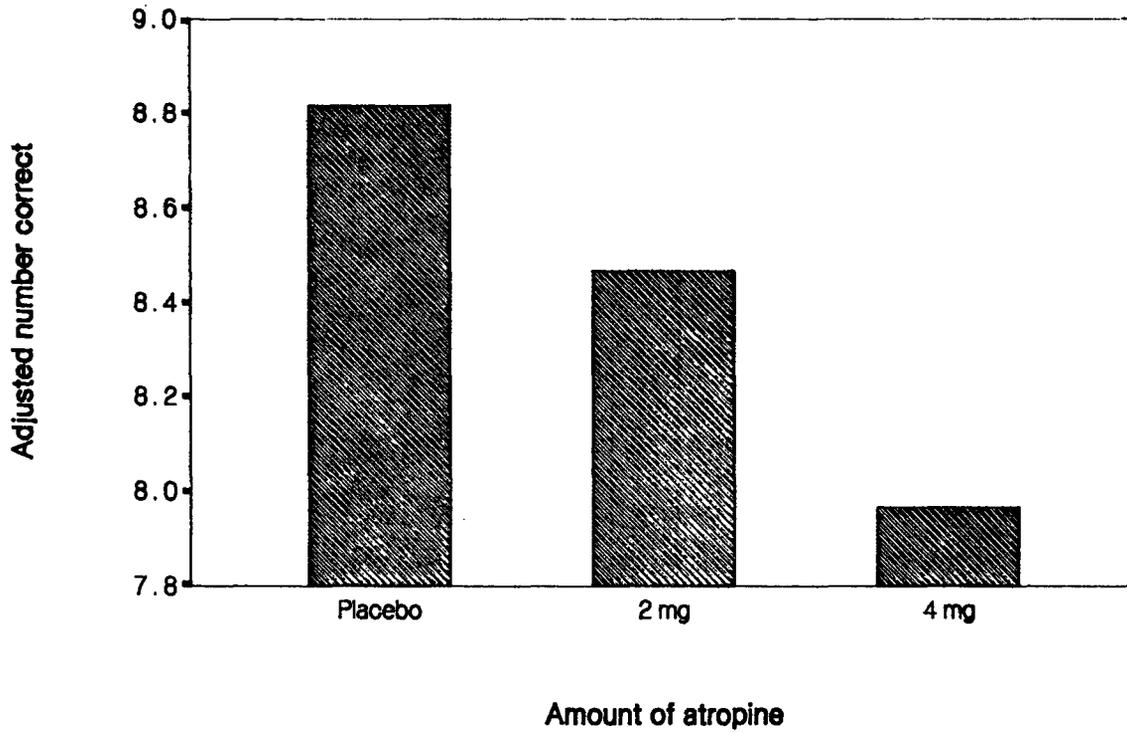


Figure 23. Dose main effect on number correct during the six-letter search task of the PAB.

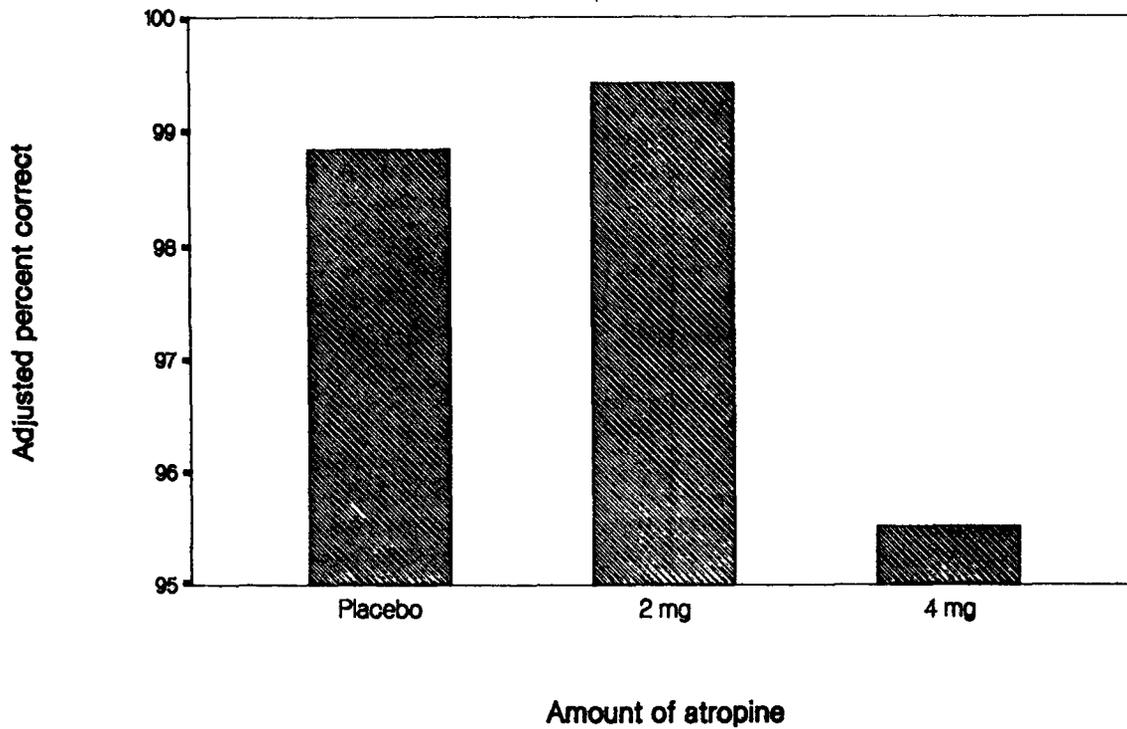


Figure 24. Dose main effect on percent correct during the six-letter search task of the PAB.

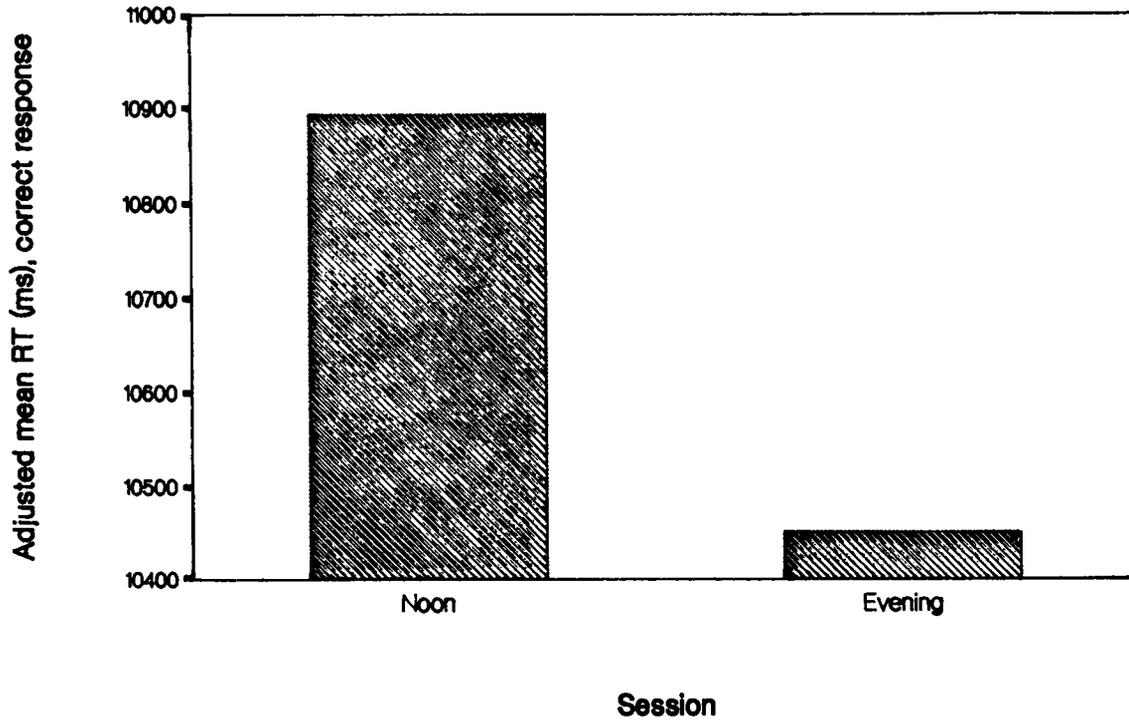


Figure 25. Session main effect on mean RT for correct responses during the six-letter search task of the PAB.

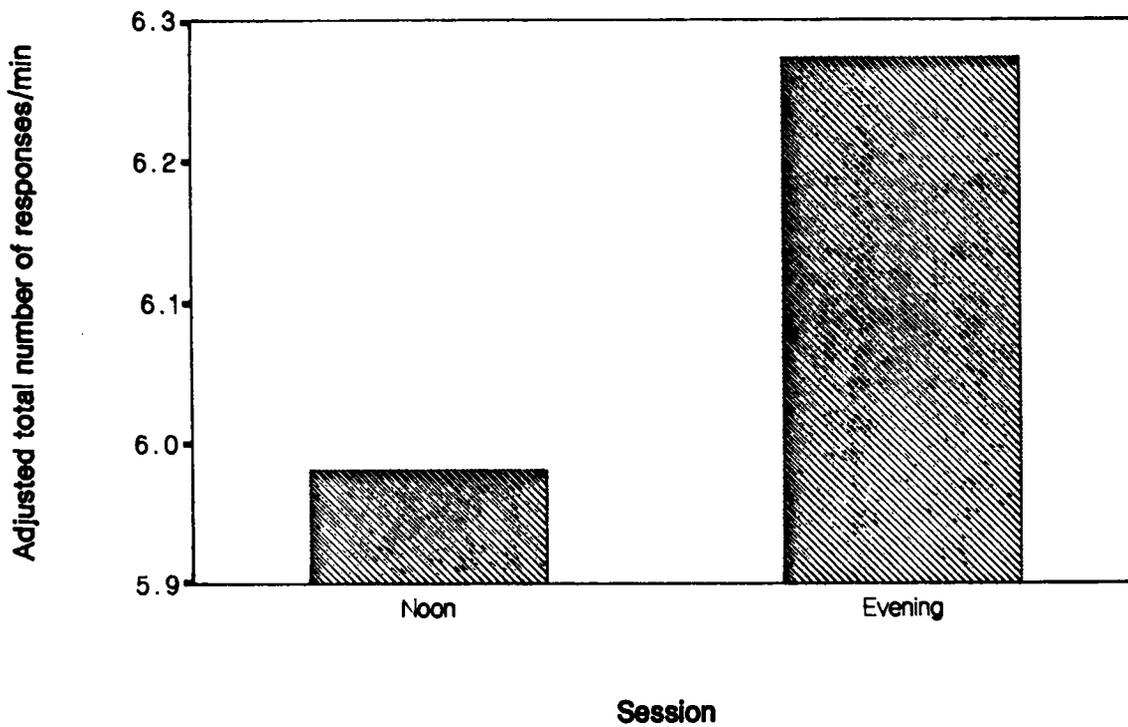


Figure 26. Session main effect on total number of responses/min during the six-letter search task of the PAB.

For the logical reasoning task, the analyses were identical to those described above. These analyses showed neither interactions nor session main effects reached significance for any of the six measures. There was a significant dose main effect for the mean RT for correct responses ($F(2,21)=5.82$, $p=.0097$); however, contrasts for this main effect (Figure 27) were unable to identify an unique source. There was a tendency for 4 mg of atropine to increase RT relative to either placebo or 2 mg atropine.

The analysis of covariance for the speed measure indicated only the dose main effect reached significance ($F(2,21)=4.15$, $p=0.0302$). Contrasts for this effect (Figure 28) indicated a slight decrease in the total number of responses/min under 4 mg of atropine compared to 2 mg of atropine ($F(1,10)=10.37$, $p=0.0276$). The results of these analyses for the number attempted, number correct, percent correct, and throughput measures revealed no significant effects.

For the serial addition/subtraction task, analysis of covariance results revealed no significant interactions. A dose main effect was observed for the number attempted measure (Figure 29) ($F(2,21)=4.01$, $p=0.0336$), but contrasts did not reach the 0.05 significance level.

Analysis of the mean RT for correct responses revealed a dose main effect ($F(2,21)=4.71$, $p=0.0205$), but contrasts for this effect (Figure 30) again failed to reach significance. Three of the remaining measures also were sensitive to the effects of atropine: percent correct ($F(2,21)=3.96$, $p=.0347$), speed ($F(2,21)=8.71$, $p=0.0018$), and throughput ($F(2,21)=7.74$, $p=0.003$). No significant differences were found with respect to the number correct.

Contrasts for the dose main effect for percent correct (Figure 31) indicated a significant reduction due to 4 mg of atropine when compared to placebo ($F(1,10)=8.83$, $p=.0420$). Contrasts for the speed dose main effect (Figure 32) revealed total speed decreased significantly for the 4 mg condition when compared to either the placebo condition or the 2 mg condition ($F(1,10)=10.72$, $p=0.0252$ and $F(1,10)=12.91$, $p=0.0147$, respectively). Contrasts for the throughput dose main effect (Figure 33) also indicated a reduction in the number of correct responses/min for the 4 mg condition compared to the placebo condition or the 2 mg condition ($F(1,10)=13.23$, $p=0.0138$ and $F(1,10)=10.69$, $p=0.0252$, respectively).

A session main effect was observed only for the speed measure (Figure 34) ($F(1,11)=5.01$, $p=.0468$). It indicated an increase in speed of responding from noon to evening sessions.

Analyses of covariance for the four-choice serial reaction time task were identical to those described above. Results of

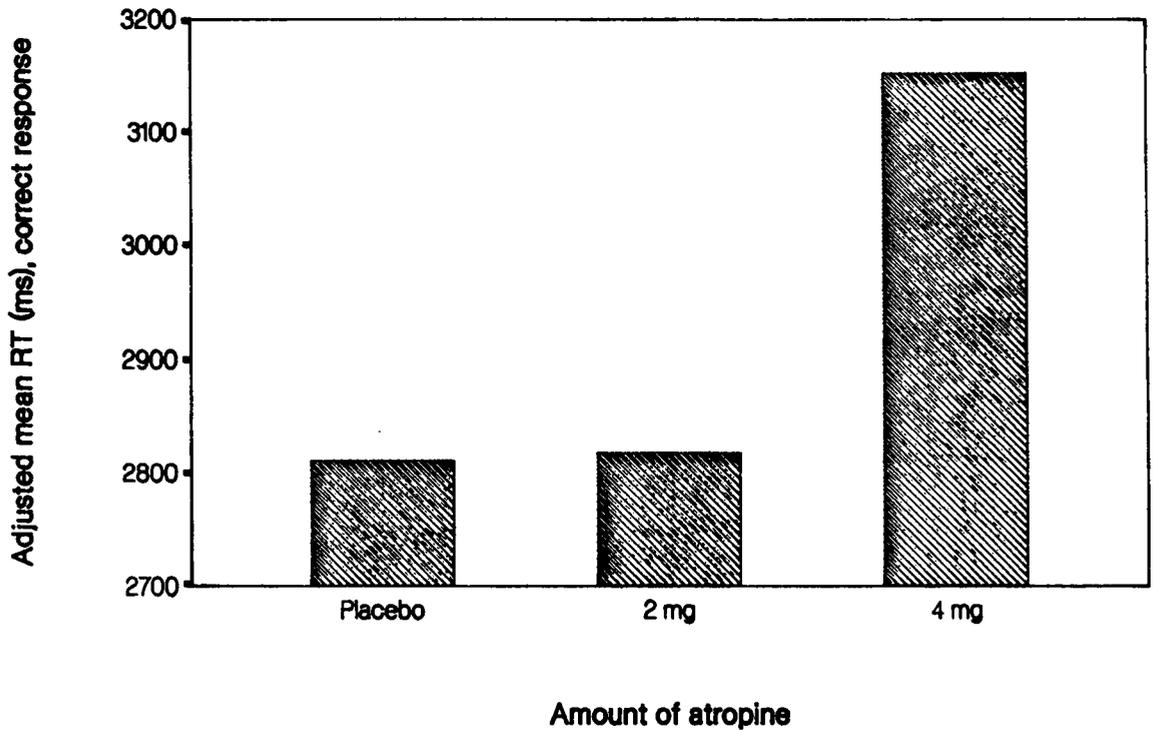


Figure 27. Dose main effect on mean RT for correct responses during the logical reasoning task of the PAB.

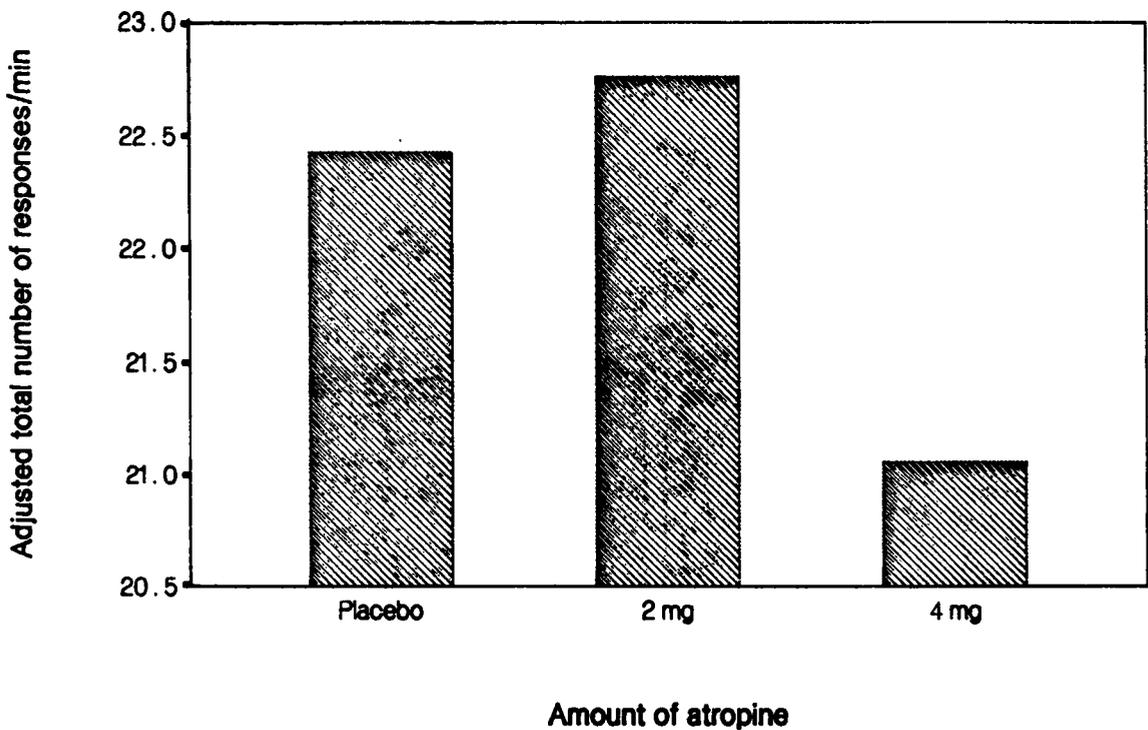


Figure 28. Dose main effect on total number of responses/min during the logical reasoning task of the PAB.

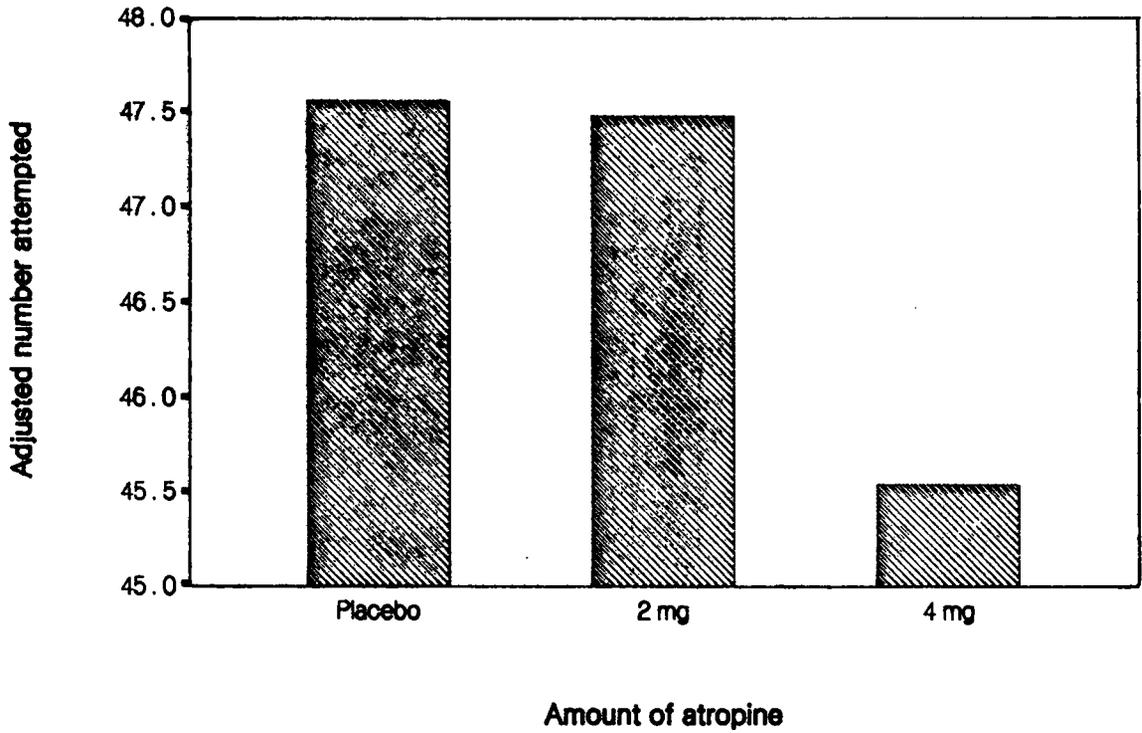


Figure 29. Dose main effect on number attempted during the serial addition/subtraction task of the PAB.

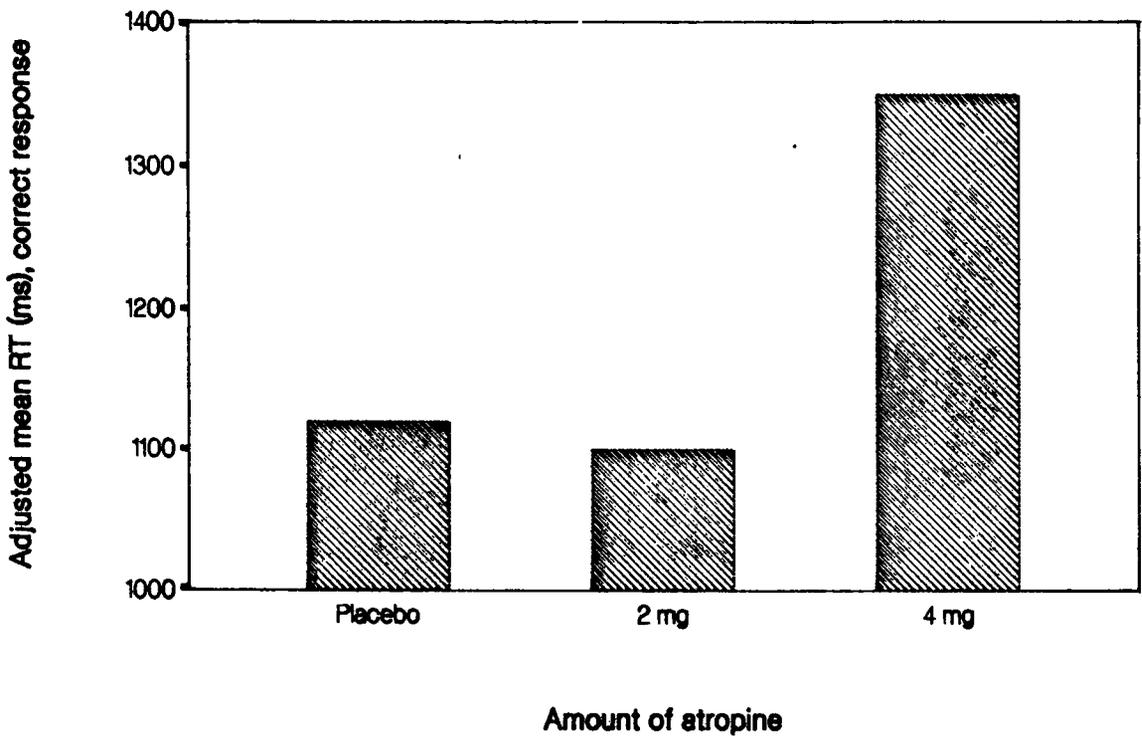


Figure 30. Dose main effect on mean RT for correct responses during the serial addition/subtraction task of the PAB.

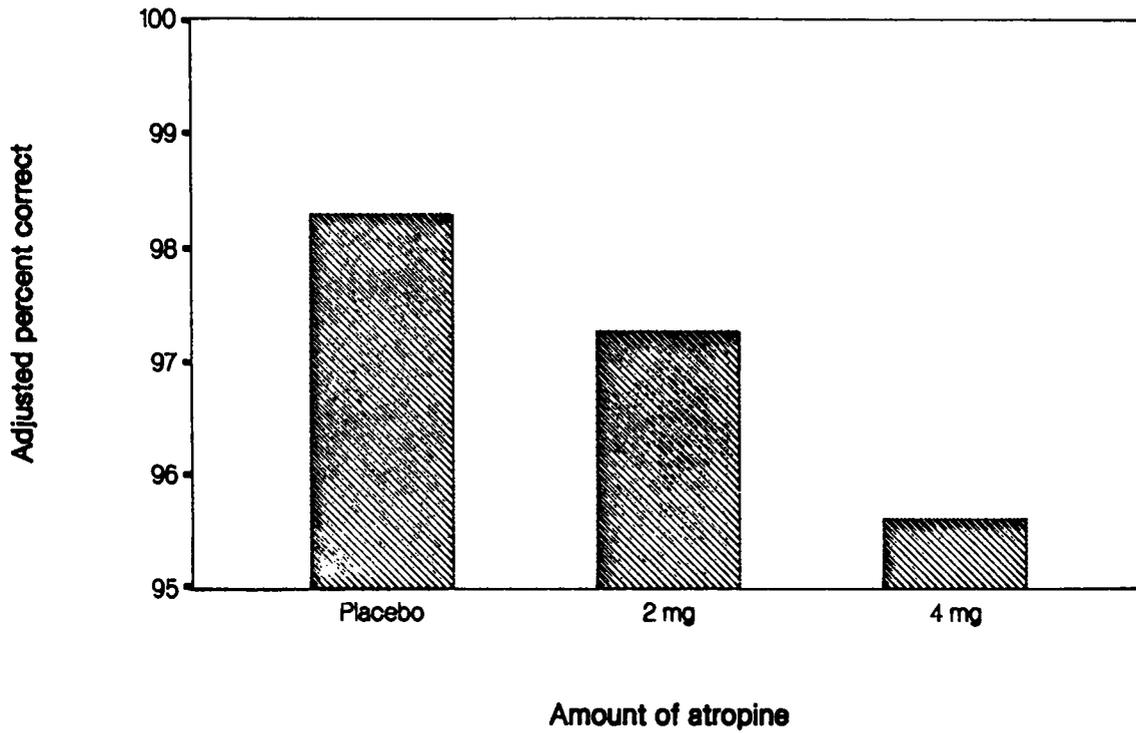


Figure 31. Dose main effect on percent correct during the serial addition/subtraction task of the PAB.

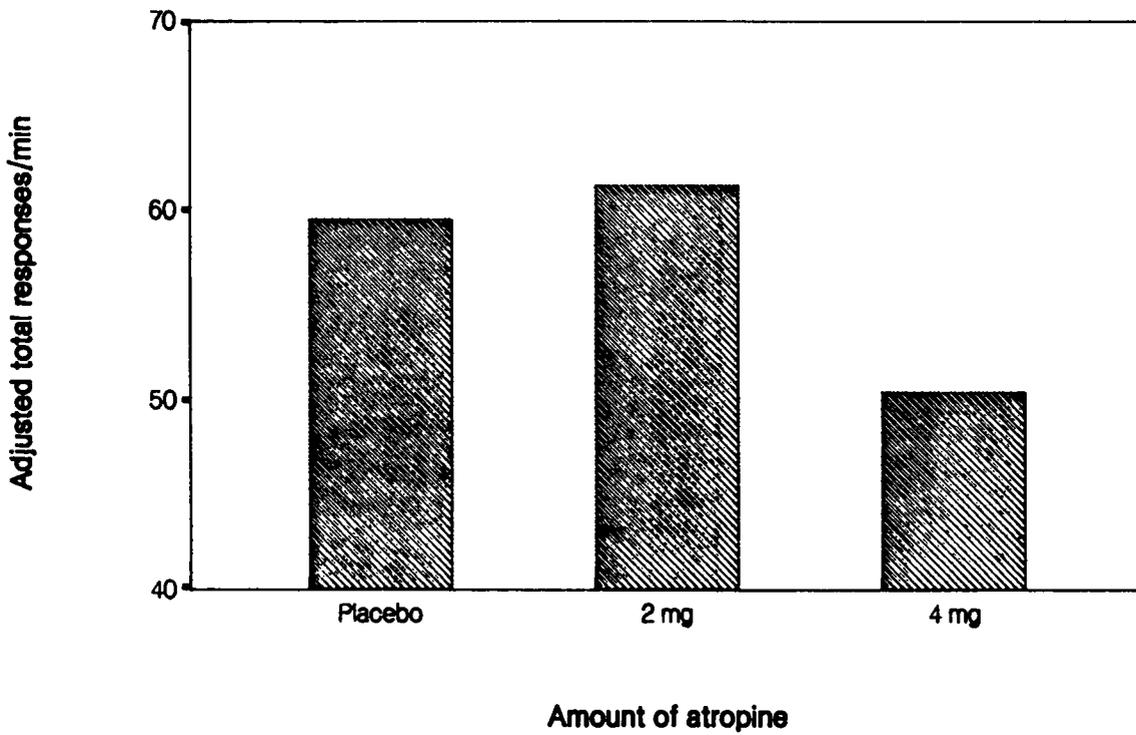


Figure 32. Dose main effect on total number of responses/min during the serial addition/subtraction task of the PAB.

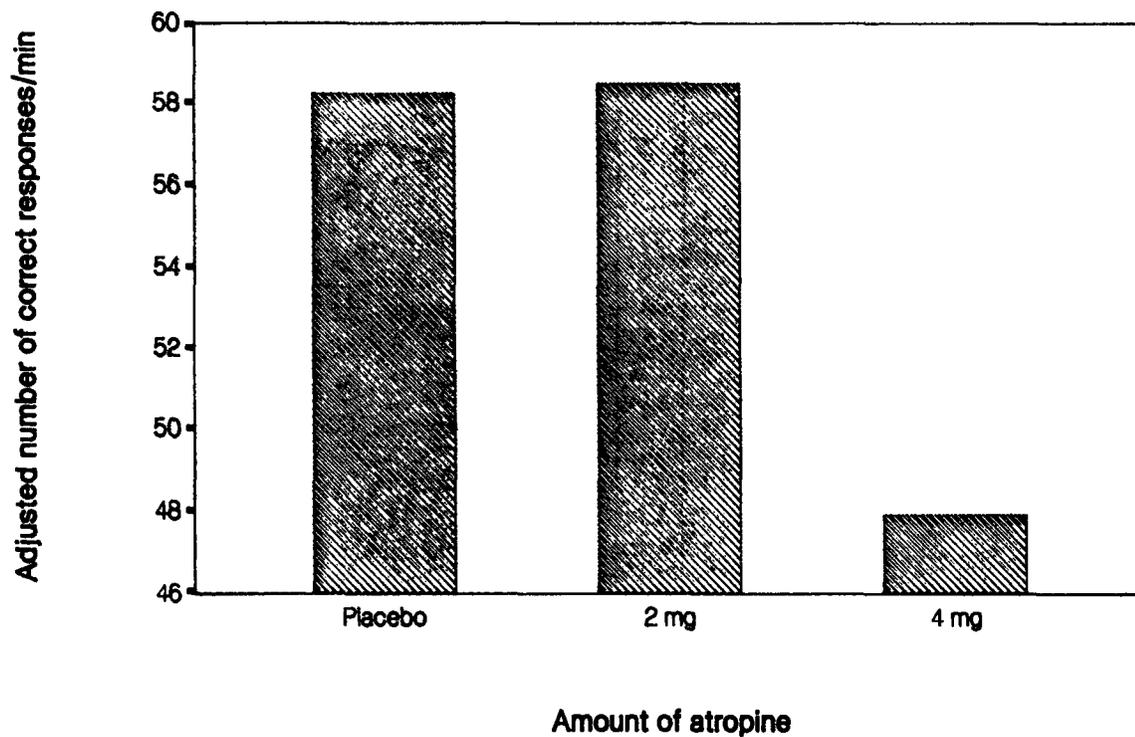


Figure 33. Dose main effect on total number of correct responses/min during the serial addition/subtraction task of the PAB.

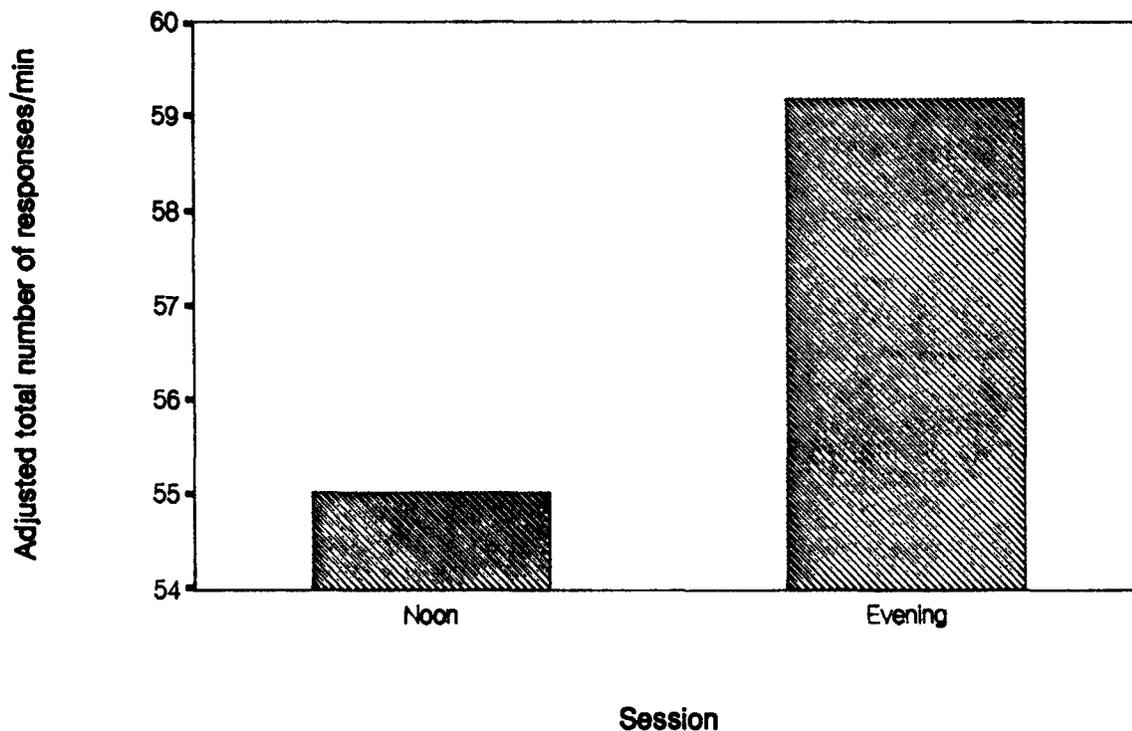


Figure 34. Session main effect on total number of responses/min during the serial addition/subtraction task of the PAB.

these analyses showed significant dose X session interactions for the number attempted ($F(2,22)=10.61$, $p=0.0006$), the number correct ($F(2,22)=14.73$, $p=0.0001$), the mean RT for correct responses ($F(2,22)=14.17$, $p=0.0001$), the speed ($F(2,22)=9.73$, $p=0.0009$), and the throughput ($F(2,22)=13.65$, $p=0.0001$).

Simple effects for the interaction for number attempted (Figure 35) revealed an increase from the noon session to the evening session at 4 mg ($F(1,11)=30.26$, $p=0.0002$). No other session comparisons were significant. Furthermore, simple effects revealed a significant dose effect at the noon session ($F(2,21)=34.95$, $p<0.0001$), but not at the evening session. Contrasts indicated a reduction in the number of items attempted during the 4 mg noon session when compared to the placebo noon session or to the 2 mg noon session ($F(1,10)=34.64$, $p=0.0006$ and $F(1,10)=46.99$, $p<0.0003$, respectively).

Simple effects for the dose X session interaction on number correct (Figure 36) indicated a significant increase from the noon session to the evening session at 4 mg ($F(1,11)=33.71$, $p=0.0001$). Further, there was a dose effect at the noon sessions ($F(2,21)=34.29$, $p<0.0001$), but not at the evening sessions. Contrasts performed on cell means for the noon session revealed significant reductions in the number correct for placebo versus 2 mg ($F(1,10)=9.22$, $p=0.0375$); for placebo versus 4 mg ($F(1,10)=36.13$, $p=0.0003$); and for 2 mg versus 4 mg ($F(1,10)=37.30$, $p=0.0003$).

Simple effects for the dose X session interaction for mean RT for correct responses (Figure 37) indicated a difference at the 4 mg dose resulting from a reduction in latency of correct responses from the 4 mg noon session to the 4 mg evening session ($F(1,11)=30.39$, $p=0.0002$). Also, there was a dose effect at the noon session ($F(2,21)=24.39$, $p<0.0001$), but not at the evening session. Contrasts for the noon dose effect indicated 4 mg of atropine slowed RT for correct responses compared to placebo ($F(1,10)=23.58$, $p=0.0021$) and compared to 2 mg ($F(1,10)=35.35$, $p=0.0003$).

Simple effects for the dose X session interaction for speed (Figure 38) revealed a session effect for the 4 mg dose ($F(1,11)=28.65$, $p=0.0002$), indicating a significant increase in the total number of items completed per minute from the 4 mg noon session to the 4 mg evening session. Also, there was a significant dose effect at the noon session ($F(2,21)=38.23$, $p<0.0001$). Contrasts indicated the effect was due to the differences between the 4 mg noon condition and both the placebo noon condition ($F(1,10)=39.05$, $p=0.0003$) and the 2 mg noon condition ($F(1,10)=48.18$, $p<0.0003$).

Simple effects for the interaction on throughput (Figure 39) revealed a significant session effect for the 4 mg dose condition ($F(1,11)=32.24$, $p=0.0001$). The number of correct responses/min

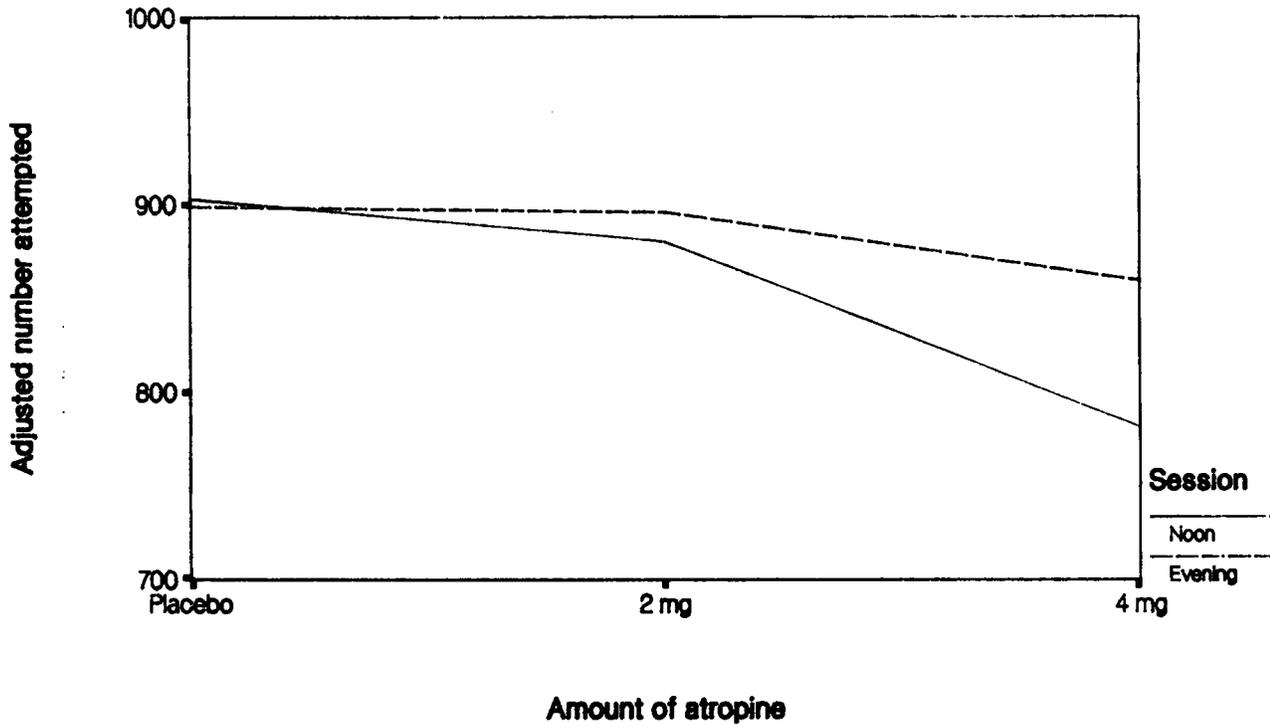


Figure 35. Dose X session interaction for number attempted during the four-choice serial reaction time task of the PAB.

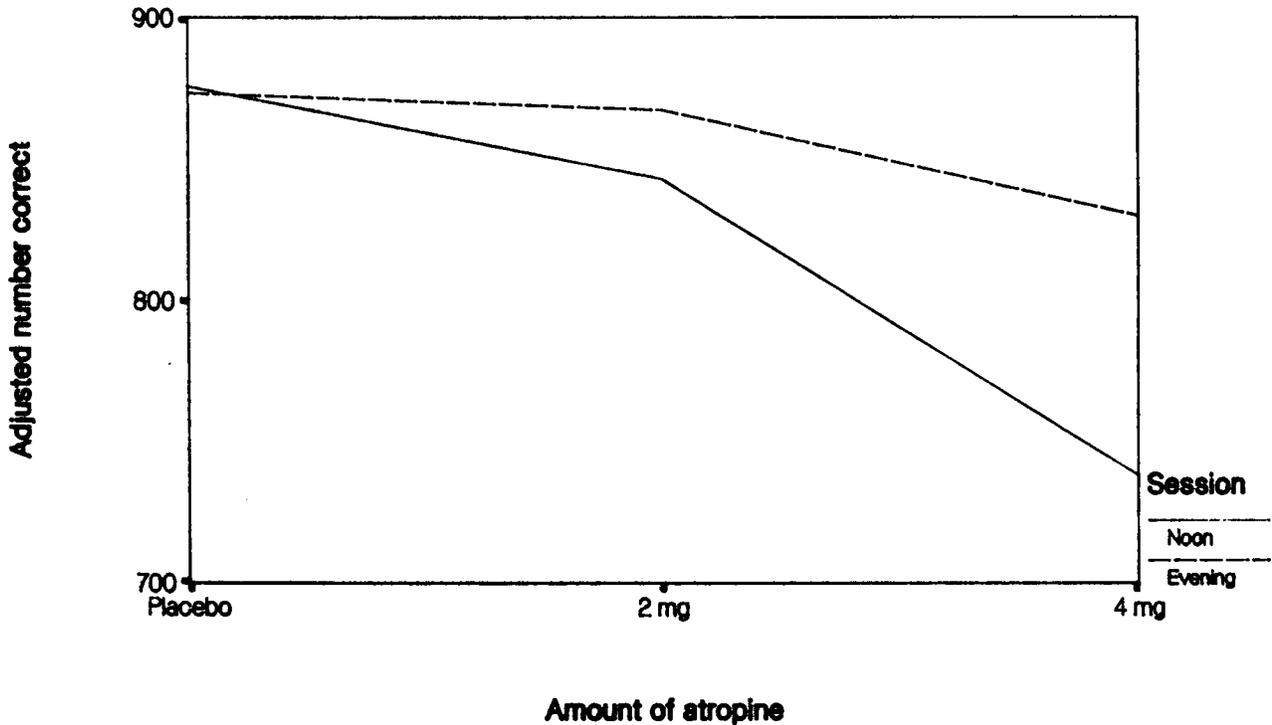


Figure 36. Dose X session interaction for number correct during the four-choice serial reaction time task of the PAB.

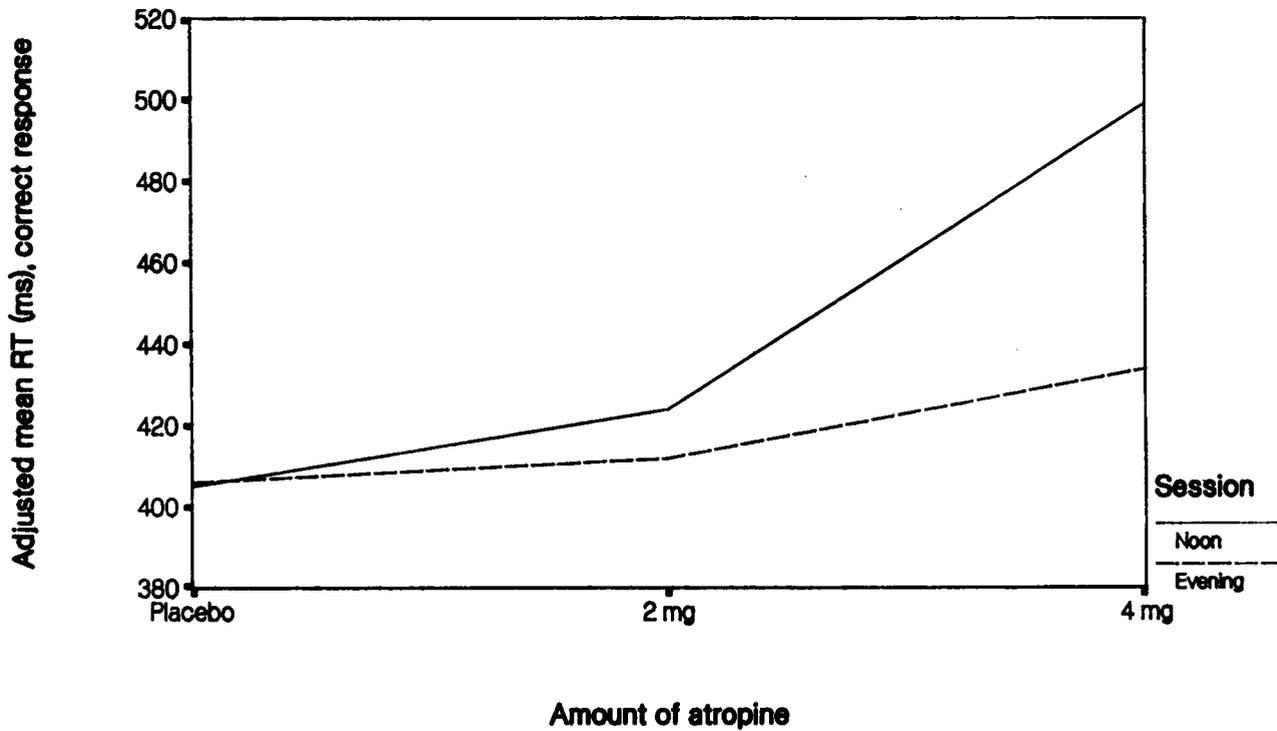


Figure 37. Dose X session interaction for mean RT for correct responses during the four-choice serial reaction time task of the PAB.

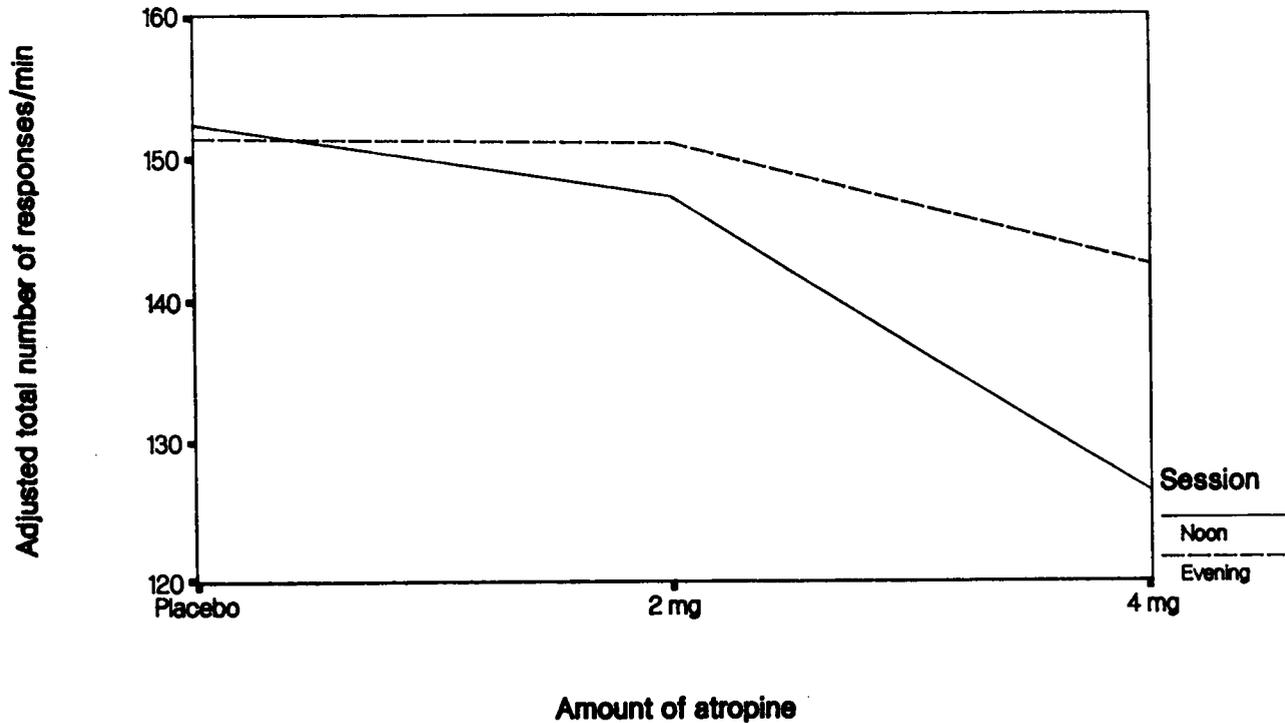


Figure 38. Dose X session interaction for total number of responses/min during the four-choice serial reaction time task of the PAB.

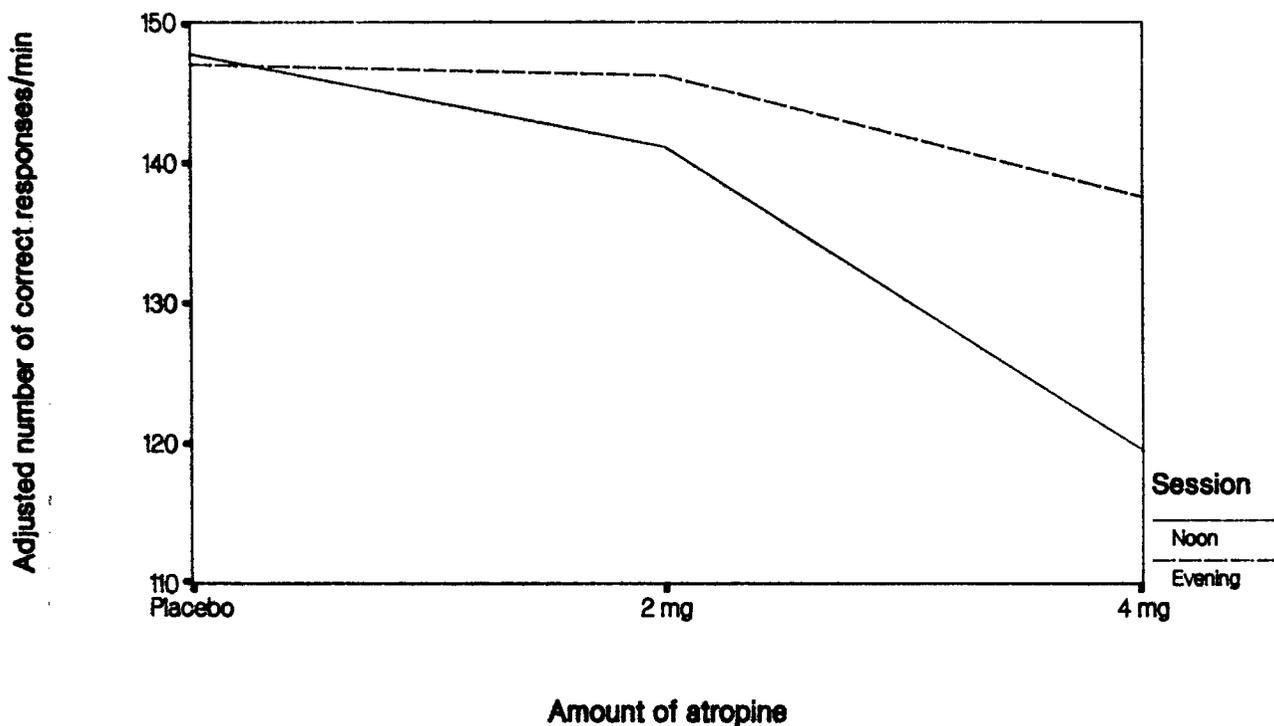


Figure 39. Dose X session interaction for total number of correct responses/min during the four-choice serial reaction time task of the PAB.

increased to 137.60 during the evening session from 119.51 during the noon session.

Simple effects also revealed a dose effect at the noon session ($F(2,21)=39.05$, $p<0.0001$), and a dose effect at the evening session ($F(2,21)=3.88$, $p=0.0369$). Contrasts for the dose effect at noon indicated a significant decrease in the number of correct responses/min with increasing doses of atropine. For placebo versus 2 mg ($F(1,10)=10.27$, $p=0.0282$), mean throughput dropped to 141.12 correct responses/min from 147.72 correct responses/min. Also, the differences between placebo and 4 mg ($F(1,10)=41.01$, $p=0.0003$), and between 2 mg and 4 mg ($F(1,10)=41.65$, $p=0.0003$), were significant.

Contrasts for the dose effect at evening showed a difference between the placebo session and the 4 mg session ($F(1,10)=10.50$, $p=0.0267$). Throughput dropped to 137.60 correct responses/min for the 4 mg evening session from 146.98 correct responses/min for the placebo evening session. None of the other contrasts were significant.

Results of the analysis also revealed significant dose main effects for the number attempted ($F(2,21)=18.53$, $p<0.0001$), the number correct ($F(2,21)=18.61$, $p<0.0001$), mean RT for correct responses ($F(2,21)=13.16$, $p=0.0002$), speed ($F(2,21)=20.78$, $p<0.0001$), and throughput ($F(2,21)=21.34$, $p<0.0001$). Contrasts

for these main effects confirm the patterns seen in the breakdown of the interactions. The 4 mg condition was worse than either the placebo condition or the 2 mg condition in all cases.

Significant session main effects were seen for number attempted ($F(1,11)=32.33$, $p=0.0001$), number correct ($F(1,11)=23.12$, $p=0.0005$), mean RT for correct responses ($F(1,11)=27.22$, $p=0.0003$), percent correct ($F(1,11)=7.99$, $p=.0165$), speed ($F(1,11)=32.71$, $p=0.0001$), and throughput ($F(1,11)=26.84$, $p=0.0003$). Examination of means revealed the same pattern of results seen in the interpretation of the interactions. Performance increased from the noon to the evening session.

Results of the analyses of covariance for the digit recall task indicated no significant interactions, dose main effects, or session main effects for any of the six dependent measures.

Taken as a whole, the results suggest atropine has its effect on cognitive performance through a slowing of processing ability. Typically, while the number correct or the percent correct measures did not reveal a significant dose effect or an interaction with dose, the mean RT for correct responses increased slightly and speed and throughput decreased somewhat with increasing doses of atropine. Exceptions to this were the six-letter search task, the serial addition/subtraction task, and the four-choice serial RT task. In the six-letter search task, the percent correct measure showed a significant dose main effect (fewer correct with 4 mg) while mean RT for correct responses did not. In the serial addition/subtraction task, both mean RT for correct responses and percent correct showed significant effects due to atropine. In the four-choice serial RT task, while mean RT for correct responses increased and speed and throughput decreased with increasing doses of atropine, the total number of correct responses also decreased with increasing doses of atropine. Apparently, subjects slowed their response rate in an attempt to maintain accuracy, especially in tasks which tapped higher-level cognitive functions, such as the logical reasoning and serial addition/subtraction tasks.

Zero input tracking analyzer

Analysis of variance of the ZITA data for morning sessions revealed a significant practice effect for all tracking task/auxiliary distraction task (task/ADT) combinations ($p < 0.05$ in all cases). To correct for this practice effect in all subsequent analyses, each subject's morning score for a particular task/ADT combination was used as a covariate in an analysis of covariance (ANCOVA). The dependent variable was a computer-generated score which ranged from 0 to 9999. It measured the time integration of the absolute distance of the tracking spot from the target. Zero represents a perfect score, and a score of 1000 represents an

average deflection of 1 cm for 30 seconds (Norman K. Walker Associates, n.d.).

The basic design of this portion of the investigation was based upon recommendations of the manufacturer (Norman K. Walker Associates, 1983), except the level 0 portions were deleted. While levels 1, 2, and 3 were well represented, the task/ADT combinations were unbalanced because tracking task 3 was not combined with the ADT of one tone every second (ADT1).

It should be noted also, the recommended design of the ZITA portion of the experiment resulted in an unbalanced number of repeated presentations of each of the task/ADT combinations. Some task/ADT combinations were repeated as many as six times per session, while others were administered only once per session. However, results of a correlation analysis revealed moderate to high correlations ($r=0.65$ to 0.86) among the repeated instances of each task/ADT combination within a session. Therefore, all subsequent analyses were based on a mean score averaged across the repeated instances of each task/ADT combination within a session.

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. Thus, it was necessary to perform a separate analysis for each of the three tracking tasks.

The analysis performed for task 1 was a $3 \times 2 \times 3$ ANCOVA with repeated measures on each of the three factors; dose (placebo, 2 mg, and 4 mg), session (noon and evening), and ADT (no tones, 2 sec/tone, and 1 sec/tone). The covariate employed was the score obtained at each day's morning session which corresponded to the scores obtained at the same day's noon and evening sessions for each task/ADT combination. For example, the score obtained on task 1/ADT0 during the morning session of the 2 mg dose day served as the covariate for scores obtained on task 1/ADT0 during the noon and evening sessions of the 2 mg dose day.

Results of this analysis revealed no significant interactions among the factors; but, the main effect of dose was significant ($F(2,21)=8.25$, $p=0.0023$), as were the main effects of session ($F(1,11)=12.13$, $p=0.0051$) and ADT ($F(2,21)=3.70$, $p=0.0421$). Contrasts performed on the adjusted mean scores of the three dose conditions (Figure 40) revealed better performance under the placebo dose than under the 4 mg dose ($F(1,10)=11.92$, $p=0.0186$) and better performance under the 2 mg dose than under the 4 mg dose ($F(1,10)=9.95$, $p=0.0309$). There was no significant difference between ZITA scores under placebo and 2 mg.

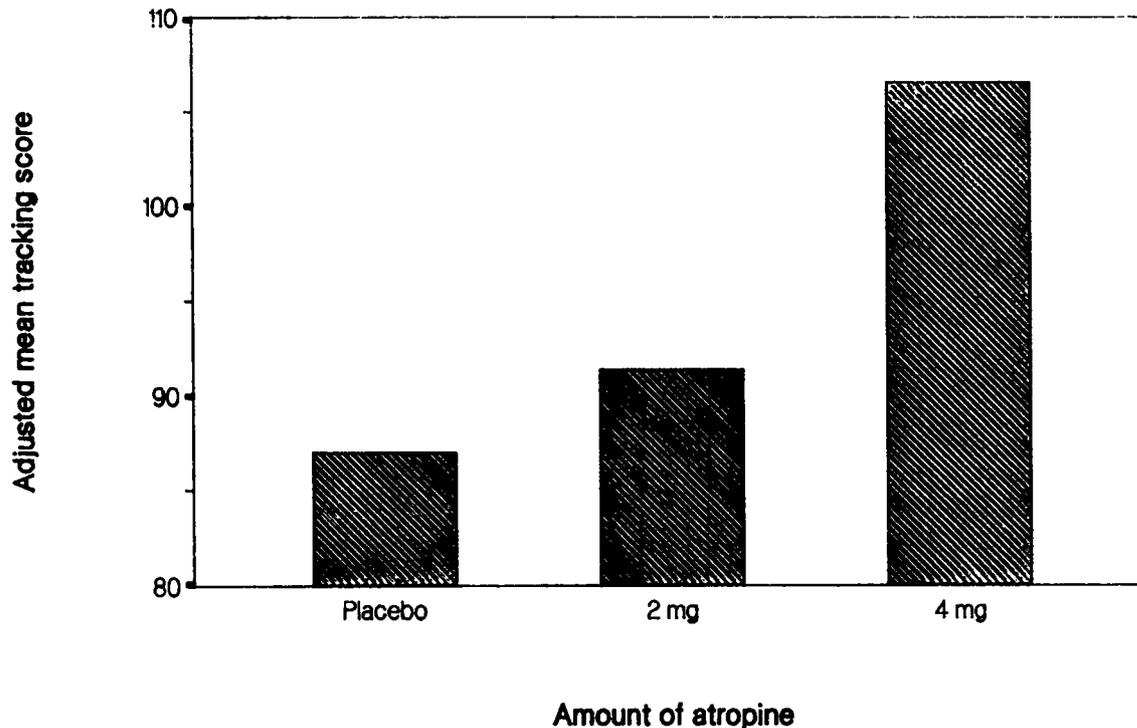


Figure 40. Dose main effect on mean tracking score for ZITA, task 1.

The significant session main effect of task 1 (Figure 41) indicated improved tracking during the evening session relative to the noon session regardless of dose or level of ADT. Contrasts for the ADT main effect (Figure 42) found no significant differences; however, examination of the means suggested a consistent trend toward degradation of tracking ability with increasing ADT demands. The adjusted mean scores were 85, 92, and 107, respectively, for ADT0, ADT2, and ADT1.

The analysis performed for task 2 was also a 3 X 2 X 3 analysis of covariance with repeated measures on each of the three factors (dose, session, and ADT). The covariate was again the score obtained during the morning session for each particular task/ADT combination. The results of this analysis revealed a significant main effect for dose ($F(2,21)=5.66$, $p=0.0108$). Contrasts for this effect found no significant differences; however, examination of the adjusted mean scores (Figure 43) showed performance tended to be worse in the 4 mg condition than in either the placebo condition or the 2 mg condition. Tracking ability again improved from noon to evening as indicated by a significant session main effect shown in Figure 44 ($F(1,11)=10.75$, $p=0.0073$). None of the interactions or other main effects were significant.

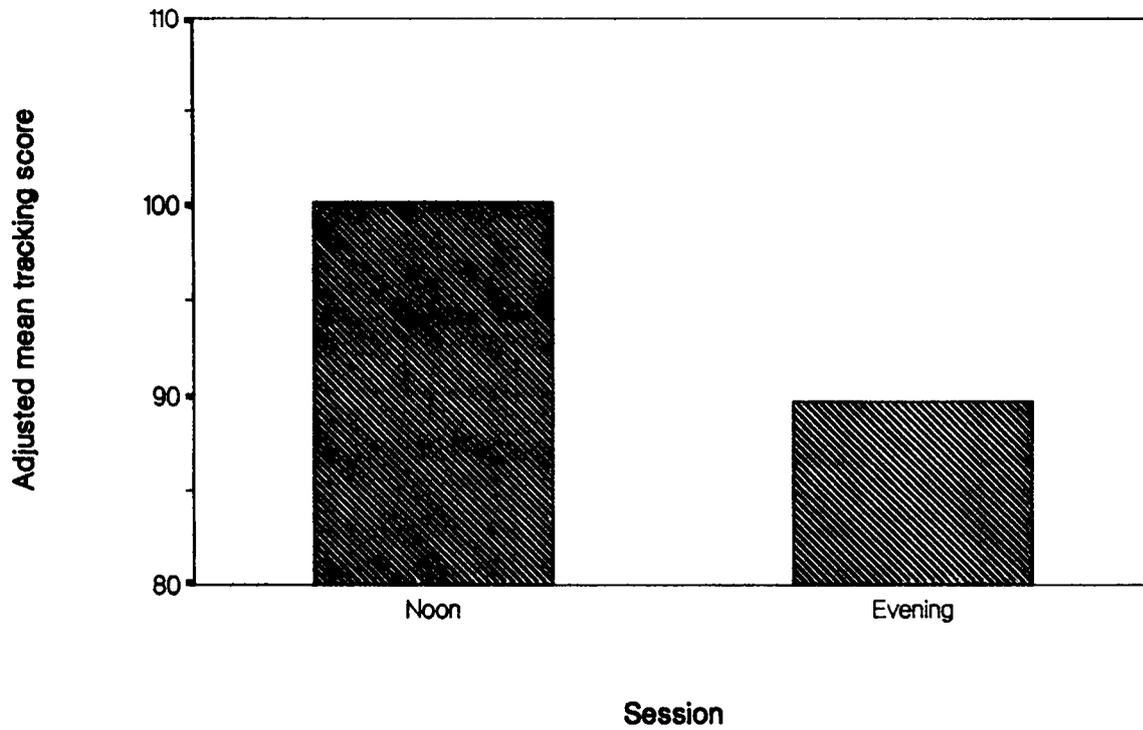


Figure 41. Session main effect on mean tracking score for ZITA, task 1.

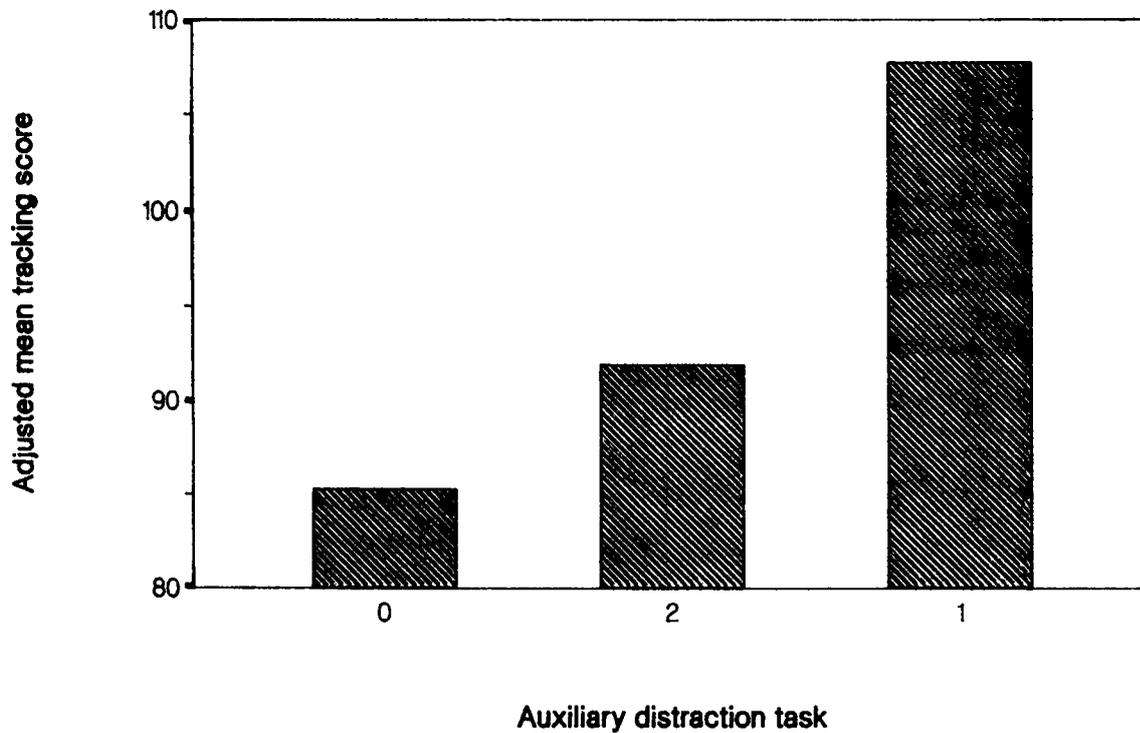


Figure 42. ADT main effect on mean tracking score for ZITA, task 1.

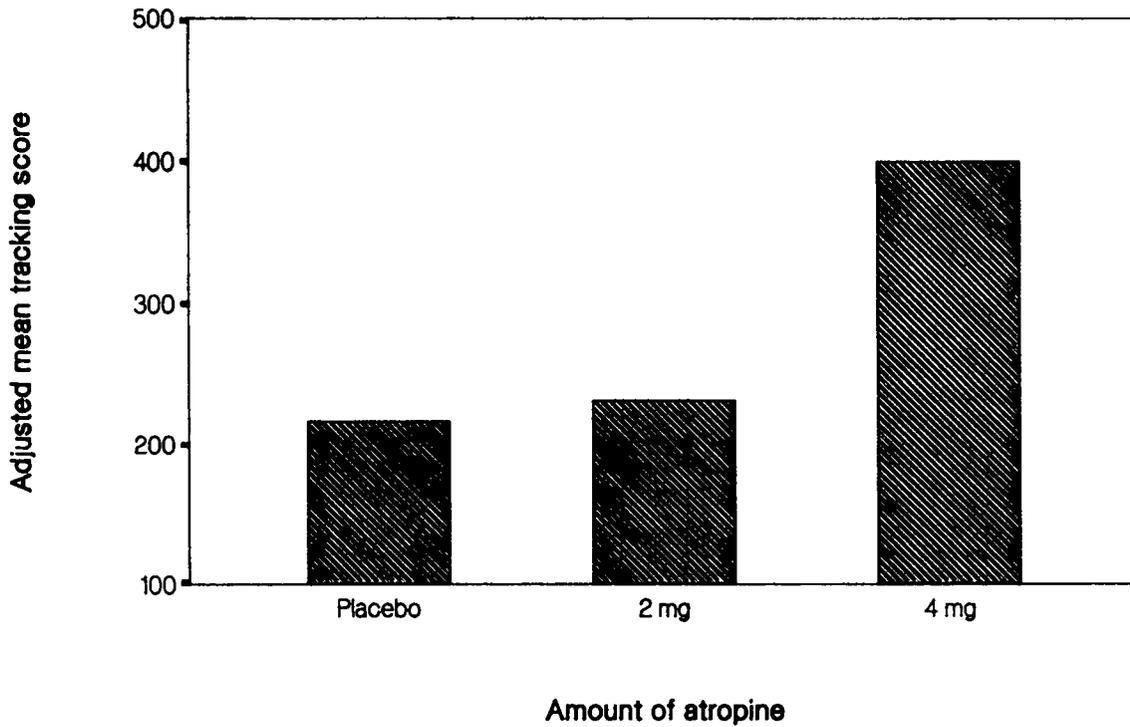


Figure 43. Dose main effect on mean tracking score for ZITA, task 2.

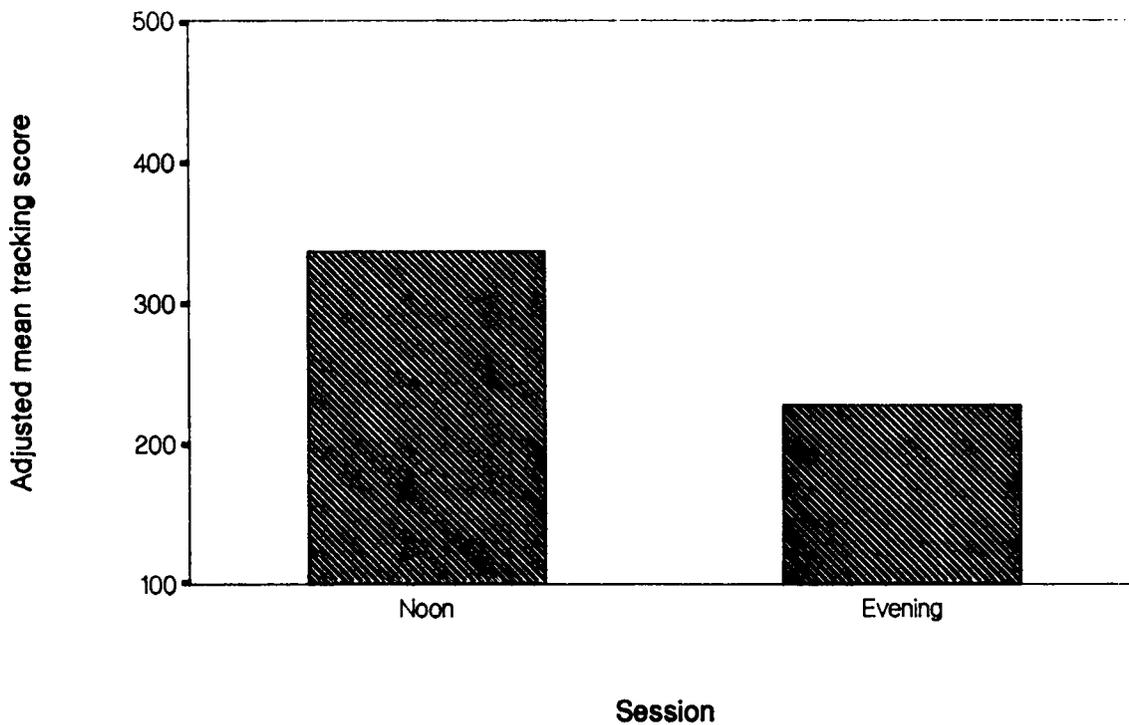


Figure 44. Session main effect on mean tracking score for ZITA, task 2.

The analysis for task 3 involved a 3 X 2 X 2 analysis of covariance with repeated measures on each of the three factors. The covariate was again the morning session score. The dose X session interaction and the session main effect were significant ($F(2,22)=7.07$, $p=0.0043$ and $F(1,11)=38.16$, $p=0.0001$, respectively). With respect to the interaction (Figure 45), simple effects indicated there was improvement from noon to evening in the 2 mg condition ($F(1,11)=9.07$, $p=0.0118$), and in the 4 mg condition ($F(1,11)=27.27$, $p=0.0003$), but not in the placebo condition. Furthermore, there was a significant dose effect at noon ($F(2,21)=5.51$, $p=0.0119$), but not in the evening. Contrasting the three dose levels at noon showed tracking ability worse under the 4 mg dose than under either 2 mg ($F(1,10)=11.89$, $p=0.0063$) or placebo ($F(1,10)=5.56$, $p=0.0401$). Differences in the evening session were not significant.

With respect to the session main effect (Figure 46), tracking ability improved from noon to evening.

These results suggest increasing doses of atropine degraded performance on all three of the tracking tasks, and this degradation was most evident during the noon sessions.

Visual Evoked Potentials

Evoked potentials were scored automatically by the Cadwell 7400 using its windowing and peak selection features to identify the location of the N75, P100, and P300 components for the wave forms collected at each of the three sessions (morning, noon, and evening) for each day of testing. Then, latencies and baseline-to-peak amplitudes were stored for later analysis. Analysis of covariance using the morning baseline as the covariate for the corresponding noon and evening sessions was performed on all measures.

For the N75 and P100 components, a 3 X 2 X 6 repeated-measures ANCOVA was performed for dose (placebo, 2 mg, and 4 mg), session (noon and evening), and checksize (4 X 4, 8 X 8, 16 X 16, 32 X 32, 64 X 64, and 128 X 128). Results of this analysis for the N75 amplitude revealed a significant dose X checksize interaction ($F(4,35, 47.43)=3.35$, $p=.0148$) and a significant dose main effect ($F(2,21)=8.81$, $p=.0017$). None of the other effects were significant.

Simple effects analysis for the dose X checksize interaction indicated significant checksize simple effects for placebo ($F(5,54)=2.44$, $p=.0459$), 2 mg atropine ($F(5,54)=3.25$, $p=.0122$), and 4 mg atropine ($F(5,54)=3.18$, $p=.0138$). Furthermore, there were significant dose simple effects at 8 X 8 checks ($F(2,21)=10.37$, $p=.0007$), 16 X 16 checks ($F(2,21)=4.22$, $p=.0288$), 64 X 64 checks ($F(2,21)=5.85$, $p=.0096$), and 128 X 128 checks

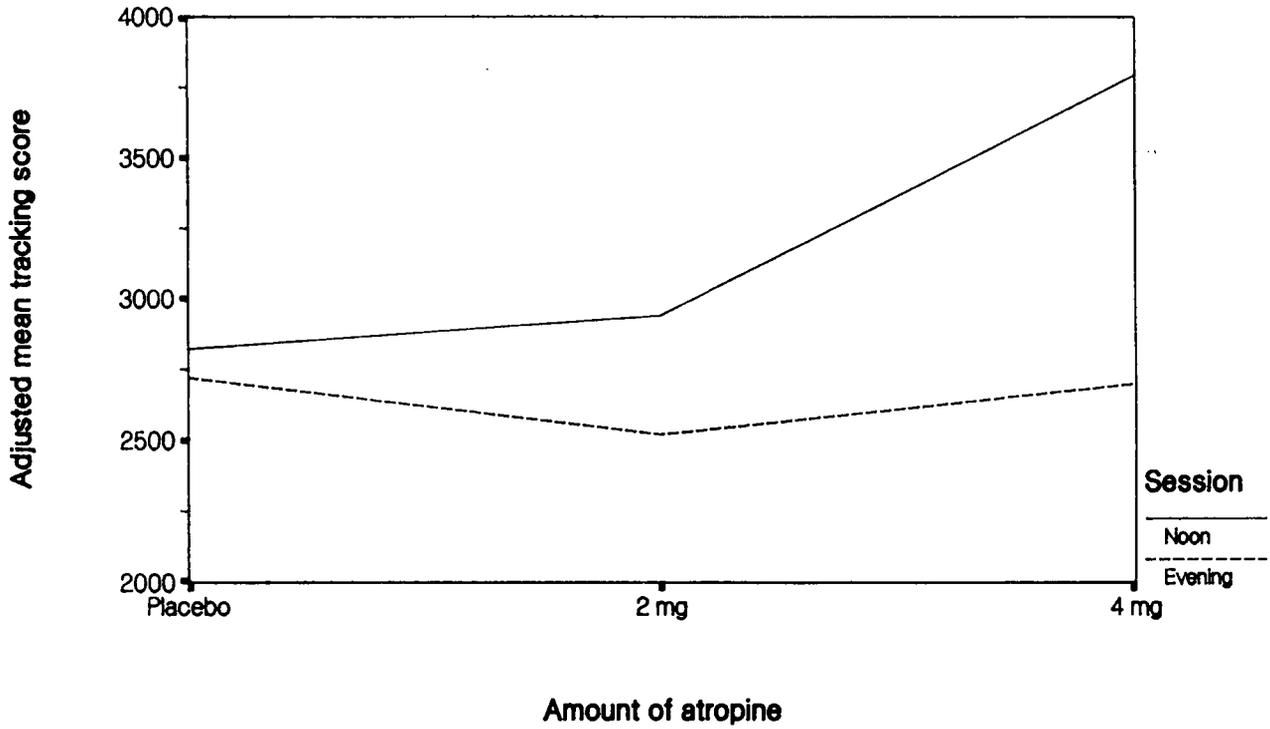


Figure 45. Dose X session interaction for mean tracking score for ZITA, task 3.

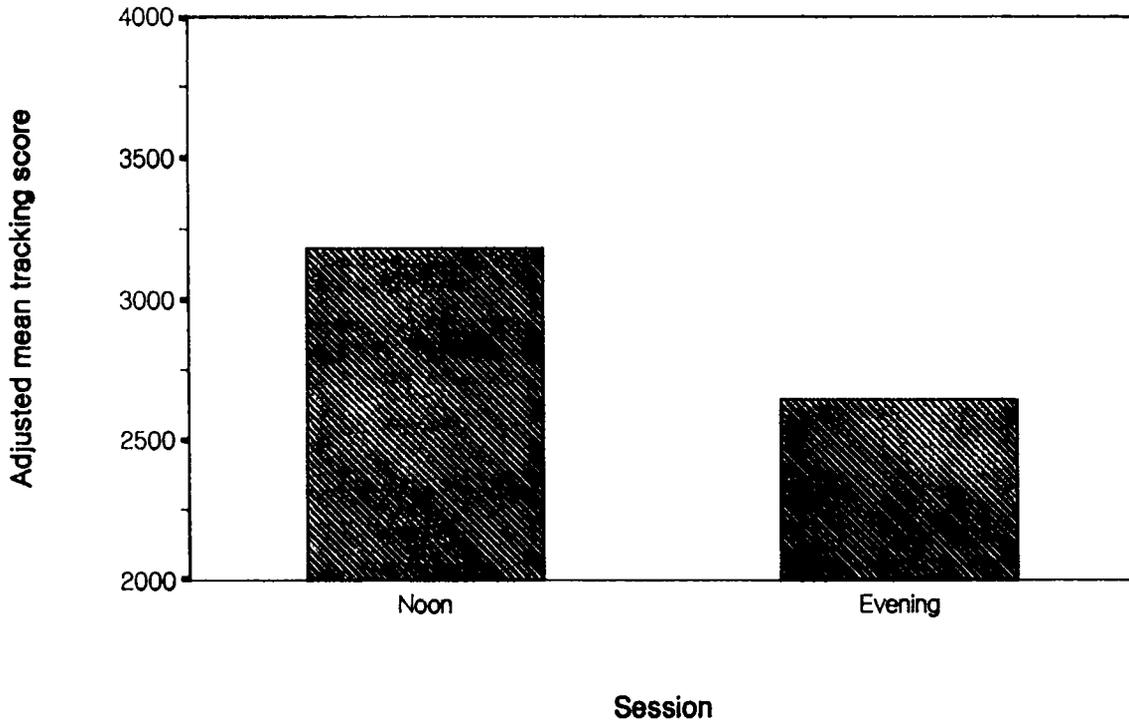


Figure 46. Session main effect on mean tracking score for ZITA, task 3.

($F(2,21)=11.07$, $p=.0005$). However, none of the contrasts for the interaction produced significant results. This obviously raises questions about the appropriateness of using Bonferroni corrections of the alpha level when the significance of the interaction and simple effects have been established.

Contrasts for the dose main effect (Figure 47) indicated 4 mg of atropine reduced N75 amplitude when compared to the effects of a placebo injection ($F(1,10)=8.93$, $p=0.0408$). None of the other comparisons were significant.

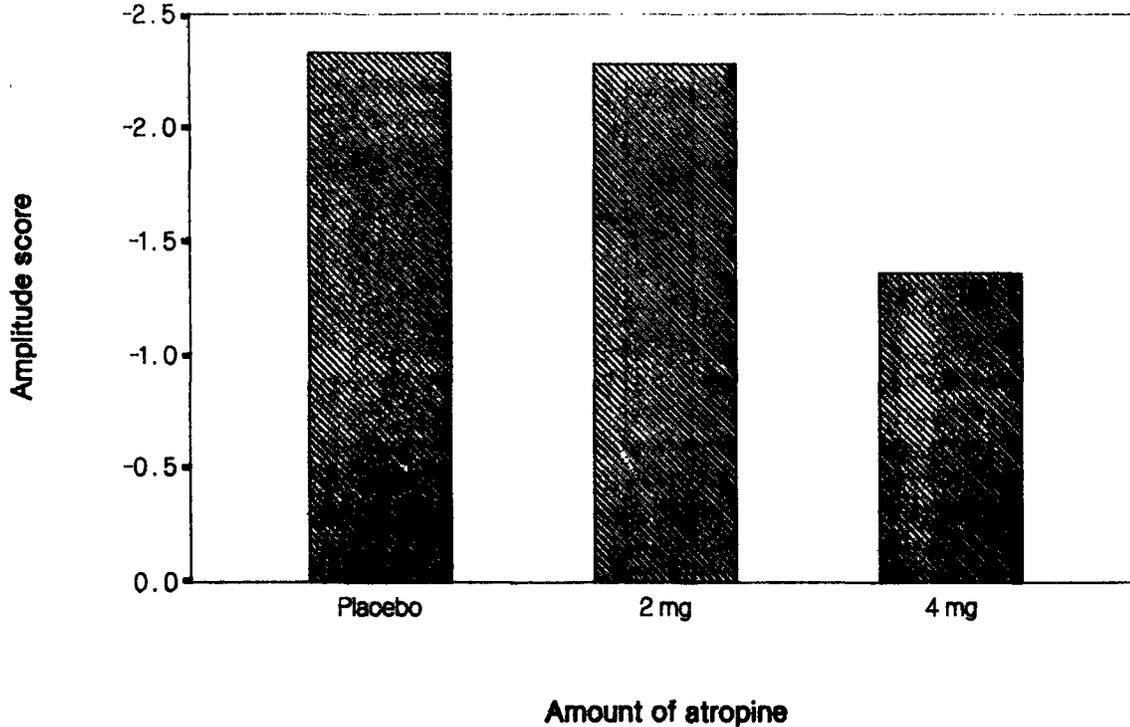


Figure 47. Dose main effect on N75 amplitude from VEP.

An identical 3 X 2 X 6 repeated-measures analysis of covariance was performed for N75 latency. Results of this analysis revealed a session main effect (Figure 48) ($F(1,11)=11.95$, $p=0.0054$). None of the other effects were significant. Subjects showed a decrease in latency during the evening session relative to the noon session.

Results of the 3 X 2 X 6 repeated-measures analysis of covariance for P100 amplitude revealed a significant checksize main effect ($F(2.11,22.74)=6.09$, $p=0.0069$), but none of the other effects were significant. In the absence of a dose X checksize interaction, differences among checksizes were considered irrelevant. Results for P100 latency revealed no significant effects.

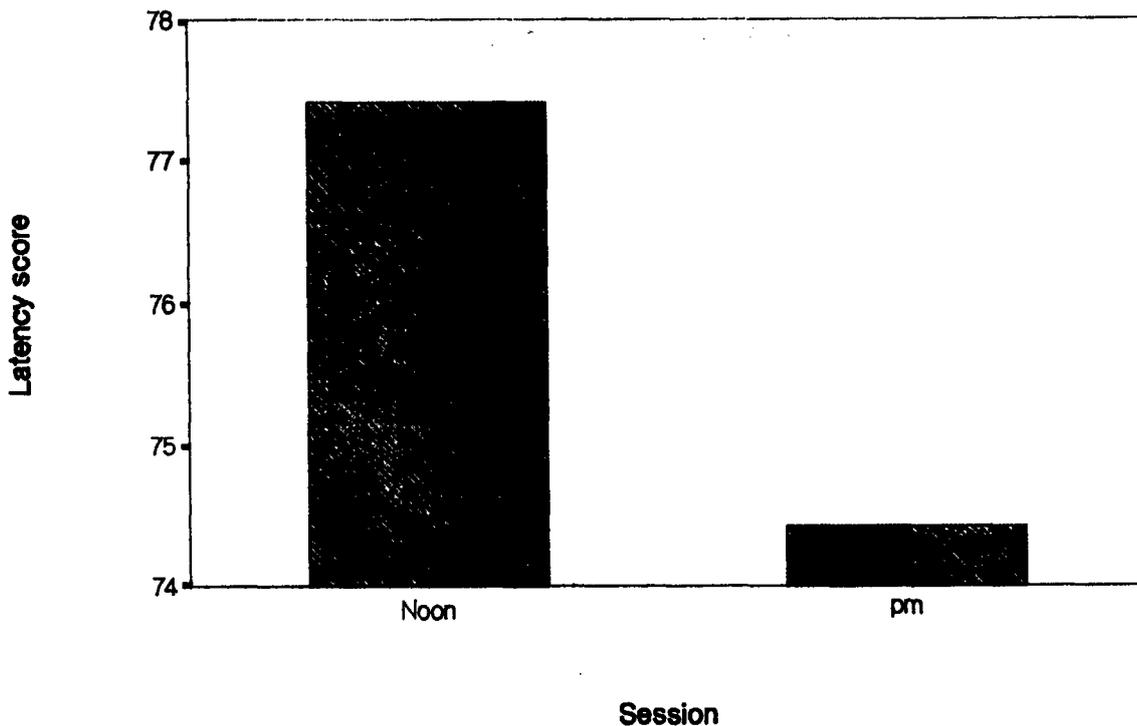


Figure 48. Session main effect on N75 latency from VEP.

The design for the P300 task was a 3 X 2 repeated-measures analysis of covariance with three levels of dose (placebo, 2 mg, and 4 mg) and two levels of session (noon and evening). Results of this analysis for P300 amplitude revealed no interaction; however, a significant dose main effect was observed ($F(2,21)=4.57$, $p=0.0225$). Contrasts for this effect (Figure 49) indicated the decrease in amplitude in the 4 mg condition was significantly different from amplitude in the placebo condition ($F(1,10)=13.27$, $p=.0135$). The session main effect was not significant. Results of the repeated-measures analysis of covariance for P300 latency indicated there was neither a significant interaction nor any main effects.

Special comment

One other finding which deserves at least some attention relates to one of the apparent side effects of atropine. During the 4 mg dose day, 8 of the 12 subjects reported some type of visual hallucination associated with viewing the TV monitors during the contrast sensitivity and the evoked response tests. These hallucinations were relatively minor and varied from subjects perceiving undefined shadows to perceiving television programs, cartoons, and still scenes (one subject reported seeing a baby on a blanket with a parachute lying next to the blanket).

No hallucinations of any type were reported outside of the visual testing environment.

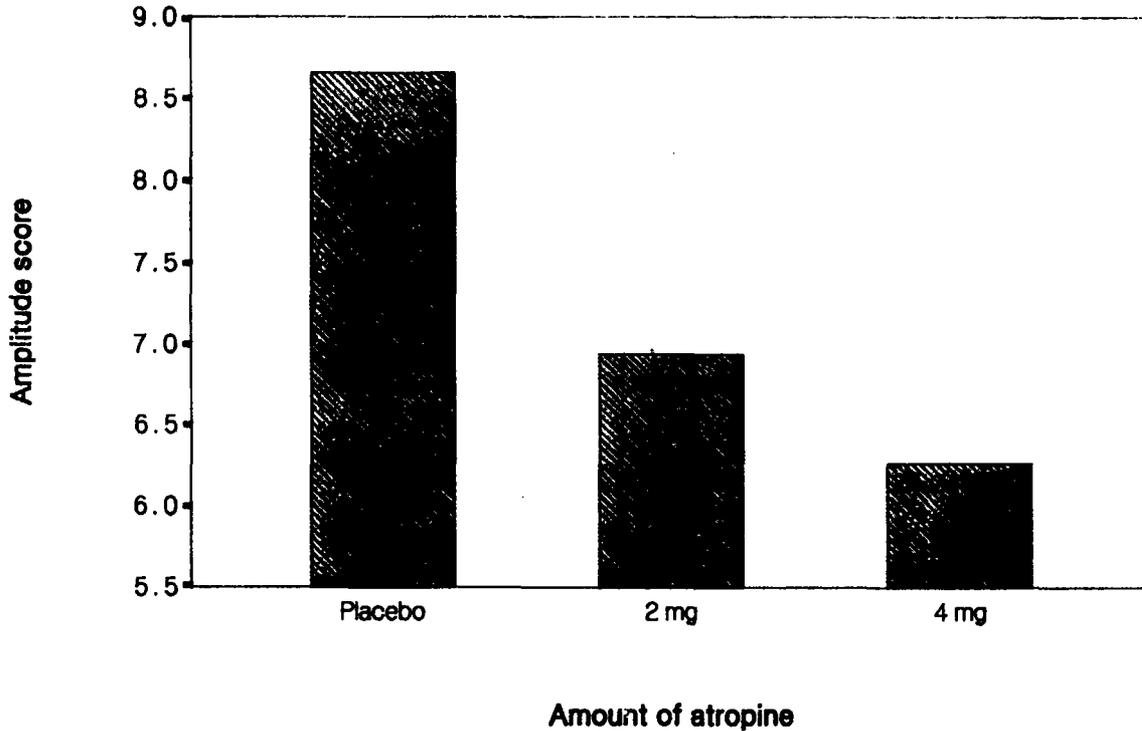


Figure 49. Dose main effect on P300 amplitude from VEP.

Discussion

Physiological measures

Heart rate

It is important to remember atropine has a different time course in the central nervous system than it has in the peripheral system. Heart rate followed the expected time course of the atropine available in the peripheral system (sometimes called the intravascular compartment). That time course should be used very cautiously to predict the time course of behaviors stemming from or significantly interacting with the central nervous system. The time course there is likely to be longer (see Gilman, Goodman, and Gilman (1980) for further discussion). In no case did heart rate exceed the medical safety cutoff of 150 bpm for 15 minutes; nor did any subject report any adverse cardiorespiratory symptoms during the study. Normal, unstressed aviators typically have heart rate increases of 9.3 ± 9.2 bpm during flight in a UH-1H (Knox et al., 1982); so, even if, due to the stresses of flight, the heart rate had increased an additional 10 bpm above the heart

rate under the influence of atropine, it still would not have been medically significant for actual flight. Holter monitor recordings did not signal any cardiac rhythm irregularities; in fact, variability of heart rate characteristically decreased during atropine effects.

Urine specific gravity

No medically significant effect on urine specific gravity was found. Subjects were able to maintain hydration within normal limits without difficulty in the laboratory environment.

Visual accommodation

The potential for examining visual accommodation to distinguish between doses of 2 and 4 mg of atropine during the first 12 hours of administration was highlighted in the study. This observation may be important operationally. In addition, there is the possibility a simple and inexpensive device like the Prince rule might be used to obtain such information in the field if a baseline for the individual is known. This possibility will be examined in detail during the next phase of this work.

Helicopter flight simulator

Subjective ratings of flight performance

Dose-related effects were consistent with what has been found with other dependent measures collected during this investigation. Performance ratings on the instrument takeoff, level flight, holding at the outer marker, and instrument landing all manifested decrements under the 4 mg atropine dose. The composite score of performance on all maneuvers combined was affected similarly. Most frequently, the 4 mg dose produced significant decrements in comparison to both the 2 mg dose and the placebo. However, holding at the outer marker was degraded under both 2 mg and 4 mg of atropine when compared to the placebo, whereas the ITO and landing were apparently unaffected by the 2 mg dose even though they were degraded significantly by the 4 mg dose. Only one maneuver, the ITO, apparently was affected by whether it occurred immediately postdose or 5 hours postdose. The observation that evening performance was worse than noon performance under the 4 mg dose on this maneuver may have resulted because the instrument takeoff always occurred early in the flight before the atropine injection had taken effect (during the morning flight), whereas the drug clearly was making its presence known by the time of the evening flight.

Objective measures of flight performance

Computerized measurements of each subject's flight performance were made in conjunction with the safety pilot ratings for the straight and level segment and the instrument landing segment. Performance was examined objectively by computer for the climbing and descending turns and the HAAT maneuvers as well. Analyses of these data revealed some atropine sensitivity on each of the simulator maneuvers with regard to at least one of the collected measures (i.e., airspeed, heading, etc.).

Vertical speed RMS errors increased during the climbing turn in the 4 mg dose condition as did heading RMS during the HAAT maneuver; and airspeed RMS, heading RMS, altitude RMS, and vertical speed RMS during the straight-and-level segment. Also, there was an increase in the RMS error for localizer needle position (only approaching significance) during the ILS, which tended to follow the same dose-response pattern observed elsewhere. In almost every instance of increased RMS error (with the exception of the climbing turn), there was a computer score decrease, representing performance decline (as would be expected).

The dose by flight interaction seen in the airspeed RMS errors during the HAAT maneuver indicated that errors were significantly lower in the morning than in the evening under placebo. This effect, in and of itself, seems explainable based on simple fatigue; however, what appeared to be taking place under 2 mg (AM worse than PM) and 4 mg (the same decrement seen under placebo) make this explanation suspect. Further, the dose by flight interaction seen in turn rate scores during the descending turn was also difficult to explain. Here, morning performance was better than evening performance under placebo, while morning performance was worse than evening performance under 4 mg. Perhaps these results were attributable to the effects of fatigue under the placebo condition, whereas they were explainable in terms of dissipating atropine effects under 4 mg. In either case, it appears there is some undetermined factor which affected these results. One possible explanation centers around learning effects (discussed earlier) which probably contributed to the overall error variance even though the linear influence of these effects was statistically removed. This possibility makes it highly recommendable that subjects be trained to an objectively verifiable level prior to treatment in future studies.

Overall, the results of computer analyses of simulator flight performance are consistent with the other data in that the 4 mg atropine dose clearly produced decrements in comparison to placebo in virtually every case where significant dose effects were found. In a majority of instances, the 4 mg dose also produced greater degradations than did the 2 mg dose. However, there were few differences between the effects of the smaller atropine dose and

the saline placebo. These findings essentially support those reported earlier by Dellinger, Taylor, and Porges (1987), who investigated the effects of 0.5 mg, 1 mg, 2 mg, and 4 mg atropine/75 kg body weight on fixed-wing simulator flight performance.

Contrast sensitivity function

Findings with regard to contrast sensitivity identified losses under 4 mg atropine averaging 35 percent for all spatial frequencies under both illumination conditions, and reaching a maximum of 52 percent at the highest spatial frequency under the presence of a glare source. Since contrast sensitivity has been shown to be a better predictor than visual acuity for some operational types of vision (Ginsburg, 1981; Ginsburg et al., 1982; Ginsburg, Easterly and Evans, 1983), a loss of sufficient magnitude would be expected to compromise an aviator's ability to carry out his mission. Flight missions often require visual target acquisition, visual recognition of navigational landmarks, and visual avoidance of hazards to safe flight.

The operational significance of the magnitude of atropine-induced performance changes found in the examination of contrast sensitivity has yet to be established. The baseline CSFs obtained approximate the 75th percentile data of a general population large-sample normative study (Ginsburg et al., 1984). Even the CSFs for the 4 mg dose and glare were very close to the normative medians without glare. Experience derived elsewhere (with an aviator developing cataracts, but still actively flying) suggests a wide variance in contrast sensitivity within which an aviator feels visually competent.

Bachman and Behar (1987) examined the effects on the CSF of cyclopentolate (which has ocular effects similar to atropine). The results were qualitatively very similar to those of systemic atropine and quantitatively nearly identical to the effects of 2 mg of atropine, even though maximum pupil dilation (8.08 mm) occurred. In the cyclopentolate study, accommodative losses were compensated with lenses (+0.36D on average), but no accommodative compensation was provided in the atropine study. As the viewing distance was 3 m, only +0.33D accommodation was required to bring the contrast sensitivity display into sharp focus on the retina. This level of residual accommodation was present even with 4 mg of atropine, and all subjects reported no difficulty in focusing for the screen distance.

The effect of 4 mg of atropine on the CSF was about twice that of topical cyclopentolate--a finding which has no explanation in terms of peripheral (i.e., ocular) changes. Hence, some of the observed changes may be attributable to the CNS effects of atropine. One of the limitations of the psychophysical procedure

employed is its vulnerability to changes in the criterion of visibility the subject uses. If atropine affects judgmental processes, it would be necessary to use other procedures (such as forced-choice) to separate changes in visibility from changes in response criterion.

The results obtained, particularly with 4 mg and with glare, may, in part, be attributable to still another central effect (which was reported by 7 of the 12 subjects plus the prestudy pilot subject), namely, the appearance of visual hallucinations referred to the contrast sensitivity display. These images apparently were so vivid most subjects thought the equipment was malfunctioning and was receiving broadcast television signals. Several reported they would not be able to perform as well because of the interference produced by these images.

Penetar and Kearney (1987) did not obtain statistically significant reductions in contrast sensitivity 2 hours after 2 mg or 4 mg injections of atropine per 70 kg body weight. Reasons for the discrepancy between their results and ours are not known; but, it may be related to one or more of the procedural differences in the two studies. Examples of these include the psychophysical methodology, ambient illumination (we used a glare source), time of testing following injection (much longer in our study), and subject workload. Penetar's subjects relaxed between injection and CSF testing, while ours flew in the simulator for 90 minutes. Also, our subjects were exposed to long series of flickering video displays (contrast and mean illumination undocumented) presented for VEP analyses just prior to the noontime CSF testing, and received a battery of cognitive and perceptual-motor tests prior to the evening CSF test.

Performance assessment battery

With the exception of the digit recall task, all subtests identified some performance degradation as a result of the 4 mg atropine dose. However, the only subtests in which the percentage of correct responses was reduced as a result of atropine were the six-letter search and serial addition/subtraction. For the other subtests (excluding digit recall), the reaction time for correct responses was lengthened under the 4 mg dose as compared to the placebo or the 2 mg dose. Likewise, the total number of items completed per minute (speed) was affected as well. On both the serial addition/subtraction subtest and the four-choice serial RT subtest, a similar measure (number of correct responses per minute) also was affected in that the 4 mg dose produced a speed-related decrement. The finding that percentages of overall correct responses were unaffected by atropine in almost every subtest, with the exception of six-letter search and serial addition/subtraction, revealed subjects were slowing their

response rates in order to preserve the accuracy of their performance rather than simply answering the items incorrectly. This approach--of trading speed in order to preserve accuracy--is consistent with other reports (e.g., Banderet et al., 1986). The decrements observed in the six-letter search and serial addition/subtraction subtests, which were not observed in other subtests, may indicate accurate performance on these particular subtests depends largely upon the subject's ability to develop and maintain a workable search-and-identification strategy which would not closely resemble strategies used in the performance of everyday tasks. Thus, conceivably, this relatively unpracticed type of performance tends to evidence deteriorations much more quickly than well-used cognitive skills or strategies of some other type.

There was a generalized trend toward improved cognitive performance from the noon session to the evening session observed with six-letter search, serial addition/subtraction, and the serial-RT subtests. A significant dose by session interaction related to one or more of the speed-related measures was observed only in the serial-RT subtest. The performance increase in the evening tended to confirm atropine effects have largely subsided by this time. For instance, there was a decrease in reaction time for correct responses and an increase in the overall number attempted, the number correct, the number of items attempted per minute, and the number of correct responses per minute from the noon session to the evening session under the influence of 4 mg of atropine for the serial RT subtest. On the other subtests, there was a straightforward time-of-day effect which may have been due to the subjects' anticipation of the completion of testing combined with some degree of practice effects.

The overall picture presented by these results shows the types of cognitive skills tapped by the five subtests used in this investigation do not simply "fall apart" as a result of atropine exposure. Rather, the subjects were able to effectively maintain accuracy of performance by reducing the speed of output. Similar results have been reported from previous investigations (e.g., Banderet et al., 1986).

Zero input tracking analyzer

The three levels of ZITA tracking tasks used to examine fine motor coordination also revealed atropine-related effects. During the least difficult tracking task, in which there was virtually no delay from stick movement to cursor response, the 4 mg atropine dose produced larger tracking errors than either the 2 mg dose or the placebo. A similar effect was found during the intermediately difficult task, although the significant dose effect apparently was not as strong as was the effect found during the first task level. During the third and most difficult task level, in which

there was delayed response accompanied by both velocity and acceleration changes in cursor movement, atropine exerted its greatest effect during the noon session in comparison to the evening session. At the noon testing time, tracking performance deteriorated significantly under the influence of 4 mg of atropine in comparison to 2 mg of atropine; and performance improved greatly from noon to evening under both 4 mg and 2 mg, whereas performance did not change under the influence of the placebo. Additionally, tracking performance routinely improved from the noon session to the evening session on each of the three tasks. The addition of an auxiliary distraction task seemed to worsen only the performance on the first task level, while performance on the other levels remained unaffected.

These findings suggest the larger dose of atropine causes performance degradations, whereas the smaller dose has few, if any, effects. The suggestion is consistent with earlier reports (Penetar and Beatrice, 1986). Based upon the knowledge gained from examining the PAB data, these tracking degradations probably are attributable to the general slowing of performance which takes place as a consequence of atropine exposure. Unlike the PAB tests in which a subject can reduce speed to maintain accuracy, the ZITA requires rapid responses to cursor movements so appropriate corrections can be made quickly to reduce overall error (cursor excursion). Thus, the slowing of responses, which worked to maintain accuracy during the largely subject-paced PAB subtests, resulted in significant degradations during the work-paced ZITA tasks. These effects are particularly relevant to our investigation since flying is primarily work-paced rather than subject-paced.

With regard to the time-course of effects on the ZITA, particularly when considering the third tracking task, one may conclude the atropine-related effects tended to be greater approximately 3 hours postdose than at 7 hours postdose, as would be predicted based on what is known about atropine metabolism. The finding that this dose by session interaction was significant only for the third task level probably resulted from the increased difficulty associated with this level in comparison to the first and second levels. As would have been expected, the task which was most demanding was the most degraded under high levels of atropine (noon session with 4 mg).

Visual evoked potentials

The effects of atropine on electrophysiological indicators of visual stimulus identification and information processing basically were consistent with expectations based on what is known about atropine effects and what was found with the PAB and ZITA.

The first evoked response task simply required subjects to

passively view the TV monitor while data concerning the early components of the responses were collected. Clearly, the amplitude of the N75 component was reduced by the 4 mg atropine dose in comparison to the placebo. Since atropine increases pupil size (increasing perceived stimulus brightness), this would lead one to expect a larger initial component under 4 mg rather than a smaller component. That this did not occur is somewhat difficult to explain. One interpretation might be that the evoked responses were showing the generalized sedative effects of atropine. Another would center around the possibility the image of the stimulus may have been slightly blurred by atropine and this caused a decrease in the N75 component, even though the increased perceived brightness of the stimulus (due to pupil dilation) probably should have caused an increase in the N75 component. An additional effect which was not dose-related was the significantly reduced latency of the N75 component from the noon session to the evening session. This latency decrease was consistent with the reduced reaction times during PAB subtests and improved ZITA performance described earlier.

The second evoked response task required subjects to count each occurrence of stimulus change evident on the TV monitor while data concerning the late component of the response were collected. Thus, in this task, the subjects were required to actively engage in some degree of information processing rather than just stimulus identification. Here, the amplitude of the P300 component also was reduced by the 4 mg atropine dose in comparison to the placebo dose.

These data suggest, beyond the possible atropine-induced problems with stimulus identification, further atropine-related effects which likely consisted of central processing degradations. While this measure (the P300) may be somewhat confounded by simple stimulus identification decrements known to occur as a result of atropine exposure, it should be noted P300 reflects the more general informational properties (like task relevance) of the stimulus rather than the physical properties (Pritchard, 1981). In fact, one study (Sokol, 1986) showed a +20 diopter lens (which completely prevented a subject from resolving the edges of horizontal and vertical gratings but did not prevent the detection of orientation), significantly attenuated P100 amplitude. The P300 wave remained, apparently unaffected.

Conclusions

Heart rate essentially duplicated published results. Differences were not medically significant during the simulator phase, but expected increased variability in the aircraft flight phase will require both on- and off-line monitoring in actual aircraft. No adverse effects are anticipated.

The key finding of the study showed a 2 mg dose of atropine sulfate caused small degradations on some of the laboratory-collected measures, but often did not produce effects which differed significantly from those produced by a placebo. However, a 4 mg dose of atropine sulfate exerted a variety of statistically significant effects upon contrast sensitivity, cognitive performance, tracking accuracy, cortical evoked responses, and simulator flight performance.

The flight performance evaluations (both subjective and objective) revealed atropine produced statistically significant changes in the subjects' abilities to fly the simulator. The safety pilot subjective ratings and the objective computer scores were in agreement concerning the degrading effects of the 4 mg dose. Results obtained from other tasks in the study suggest, further, the decrements in flight performance probably resulted from a slowing of both information processing and psychomotor performance.

The observed performance changes apparently resulted from a general slowing which occurred in response to the larger atropine dose as seen in increased reaction times with the PAB and increased tracking errors with the ZITA. Interestingly, where speed and accuracy could be traded off (as in the PAB), subjects managed to preserve the accuracy of their performance, in spite of the drug, by reducing the speed of their responses. Unfortunately, complex tracking behaviors (like flying) are not compatible with a speed-reduction strategy, since delayed response often results in larger tracking errors.

The electrophysiological data corroborated other reported data. The first series of pattern reversal tasks served to suggest subjects experienced problems identifying stimulus changes--an effect which no doubt stemmed from atropine-induced disturbances. On the other hand, the P300 task served to confirm some degree of information processing disturbance was occurring as a result of atropine exposure.

Of course, the ultimate question which remains to be answered is whether the statistically significant simulator performance degradations constitute operationally significant in-flight performance degradations. This depends on whether or not aviators will have the opportunity to trade performance speed for accuracy. The mission and the current situation usually dictate trade-offs; but, a properly prepared pilot may be able to avoid a situation calling for skills compromised by the use of atropine. With regard to cognitive performance, some slowing can be expected. With regard to tracking accuracy, most routine aviation tasks do not require tracking performance so extremely precise that moderate deviations would significantly compromise either safety or operational efficiency. This caveat may not apply, however,

to more complex tracking performance (e.g., NOE, NVG work, low-level night flight, and/or air-air combat).

As already indicated, it is difficult to draw a definitive conclusion with respect to flight performance, the most relevant behavior studied here. The safety pilot ratings are probably the most operationally interpretable portion of the flight-related data since both military and civil aviation communities routinely depend on the judgment of an experienced pilot to make a determination regarding another pilot's safety and competence. Based on these ratings, it must be concluded the administration of a large dose of atropine is likely to cause aviator performance to fall below acceptable ATM standards in a number of cases.

Degradations occurring in a relatively nonstressful environment probably will not produce large operational hazards, especially if the degradations occur during air work well above obstacles. However, the combat arena is anything but nonstressful. Both mission-related and nonmission-related factors can be involved. Ursano (1988) listed several potential sources of stress to include worries about the perceived effect of contamination itself; consideration of the impact on mission success, or even survival, as a result of possible or actual injuries or death to oneself or other crewmembers; and concerns about the welfare of one's dependents. Sleep deprivation is highly probable; its effects can be serious and are not always obvious (Haslam and Abraham, 1987). Aircraft damage during a mission is likely; the threat posed by such damage is another source of stress and may be greater than the results of the damage itself.

Several decrements were evident during instrument takeoffs and landings. Combined with the high probability that these decrements could be exacerbated by increased levels of stress should serve to caution: An overall safety compromise is likely under high doses of atropine. The decision concerning when to use atropine sulfate and how much of it to use must depend upon the precise nature of the situation in which this chemical warfare antidote is used and the potential harm to personnel which may result in certain situations if it is withheld. That decision, too, is stressful.

In the final analysis, the results of this simulator study suggest atropine sulfate administration is not likely to cause noteworthy degradations in aviator performance with a 2 mg doctrinal dose. However, with larger doses, pilots are likely to encounter problems during some phases of a mission; the more complex the mission, the greater the likelihood.

These results suggest: (1) a number of unanswered questions remain, (2) the unanswered questions can best be further investigated by conducting an in-flight study, and (3) the effects of atropine found here were not of sufficient magnitude to abandon

the idea of performing such an in-flight investigation. Therefore, it is recommended a follow-on phase be undertaken to confirm the effects of atropine sulfate on helicopter pilots in an inflight setting.

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Appendix A

Background information

Chemical threat

Nerve agents such as organophosphates are extremely potent organic compounds which inhibit cholinesterase enzymes throughout the body. Since the function of cholinesterase is to hydrolyze acetylcholine wherever it is liberated, this inhibition of the cholinesterase results in the accumulation of excessive concentrations of acetylcholine at various sites including the endings of the parasympathetic nerves to the smooth muscles of the iris, the ciliary body, the bronchi, gastrointestinal tract, bladder and blood vessels; to the secretory glands of the respiratory tract; and to the endings of the sympathetic nerves to the sweat glands. This accumulation of acetylcholine results in symptoms characteristic of muscarinic poisoning. Meanwhile, excess acetylcholine at the endings of motor nerves to voluntary muscles and in the autonomic ganglia results in nicotinic manifestations. Finally, the accumulation of acetylcholine in the brain and spinal cord results in characteristic central nervous system (CNS) symptoms. (The main muscarinic, nicotinic, and CNS signs and symptoms are shown in Table 1 on p. 2.)

Antidote

Mode of action

Atropine sulfate is the current antidote of choice for most nerve agents. Atropine does not act by preventing the release of acetylcholine. Rather, it is a competitive antagonist of acetylcholine and manifests its effects on structures enervated by post-ganglionic, cholinergic nerves such as smooth muscle, cardiac muscle, and various glandular cells. The effectiveness of this competition is greatest against the muscarinic effects of cholinergic drugs and is described as atropine's parasympatholytic or muscarinic-blocking effect.

Atropine inhibits the action of acetylcholine at all of its sites of action except in most voluntary muscles and at preganglionic synapses. As a result, atropine has a beneficial central nervous system effect on acetylcholine-induced respiratory depression. It also has an inhibitory effect on the peripheral muscarinic blockade, but has no effect on the peripheral neuromuscular paralysis caused by excessive acetylcholine; hence, its use as an antidote in organophosphate insecticide and nerve gas poisoning in combination with oximes (Ellin and Wills, 1964).

Metabolism

Intramuscularly injected atropine is relatively rapidly excreted by the human body, predominantly via the urinary tract (Kalser and McLain, 1970). Approximately one-half of a single parenteral dose appears in the urine within 4 hours. Excretion is essentially complete within 24 hours, with unchanged atropine and an inactive metabolite (a b-glucuronide) appearing in nearly equal amounts. Urinary excretion occurs at two rates, a fast rate occurring early with a $t_{1/2}$ of about 2 hours⁵ and a slow rate with a $t_{1/2}$ of somewhere between 13 and 38 hours. Intramuscularly injected atropine is absorbed rapidly into systemic circulation with measurable amounts appearing in blood within a few minutes and peaking at about 30 minutes postinjection. In comparison with blood and urine, expired air contains only low levels of atropine, at a maximum, only about 1/500 of that found in blood at an equivalent time (Kalser and McLain, 1970).

Dosage

Clinically, the dosage of atropine has ranged from the usual therapeutic dose of 0.2 to 1.0 mg (in cases of cardiac arrest, for example) as referenced by Weiner (1980), to 1000 mg or more in attempts to resuscitate patients who have absorbed huge amounts of organophosphates. Fatal overdose of atropine is rare. During atropine-comatherapy, commonly used by some psychiatric centers in the 1950s (Forrer and Miller, 1958; Kleininger, Zsadanyi, and Molnar, 1974; Lynch and Anderson, 1975), coma was produced intentionally by parenteral doses of 200 or more milligrams. Table A-1 (Weiner, 1980) shows doses of atropine and the normally expected undesirable effects.

The standard initial therapy for treatment of organophosphate poisoning is 2 mg injections every 3 to 10 minutes up to 50 mg per day (Taylor, 1980). However, in severe poisoning cases, 5000 mg treatments have been advocated (Mackey, 1982) and 11,441 mg treatments have been reported (Hopmann and Wanke, 1974). In this latter case, the patient received 0.5 mg of atropine every 20 seconds; thus, every 4 minutes the patient received 6 mg of atropine. Helm and Weger (1982) advocate use of three 2 mg doses of atropine (6 mg total) given at 10- to 20-minute intervals as a self-help therapy for nerve gas agents.

High doses of atropine can be studied safely because troublesome side effects are reversed readily by physostigmine bromide (Duvoisin and Katz, 1968; Granacher and Baldessarini, 1975; Heiser and Gillin, 1971; Johnson, Hollister, and Berger, 1981). In one

⁵The term " $t_{1/2}$ " refers to the time required to reduce a drug level in the body by 1/2.

Table A-1.

Effects of atropine in relation to dosage

Dose	Effects
0.5 mg	Slight cardiac; some dryness of mouth; inhibition of sweating.
1.0 mg	Definite dryness of mouth; thirst; acceleration of heart, sometimes preceded by slowing; mild dilation of pupil.
2.0 mg	Rapid heart rate; palpitation; marked dryness of mouth; dilated pupils; some blurring of near vision.
5.0 mg	All the above symptoms marked; speech disturbed; difficulty in swallowing; restlessness and fatigue; headache; dry, hot skin; difficulty in micturition; reduced intestinal peristalsis.
10.0 mg	Above symptoms more marked; pulse rapid and weak; iris practically obliterated; vision very blurred; skin flushed, more hot, dry, and scarlet; ataxia, restlessness, and excitement; hallucinations and delirium; coma.

Source: Weiner, 1980, p. 127.

study, Forrer and Miller (1958) reported the ability of physostigmine to reverse central and peripheral effects of a 212 mg dose of atropine; Leczycka and Trembla (1969) reported reversals of up to 700 mg doses of atropine by physostigmine. Physostigmine is inactivated in the body by cholinesterase and, since human levels of cholinesterase vary considerably in the population (Taylor, 1980), individual responses to a given dose of physostigmine may vary. As a result, when attempting to treat atropine overdoses with physostigmine, physicians must titrate physostigmine dosage against observed atropine effects.

Time course.

A markedly accelerated pulse rate was observed 15 minutes after intramuscular injection of 2 mg of atropine sulfate and

reached a maximal level about 30 minutes after injection (Cullumbine, McKee, and Creasey, 1955). The onset of dry mouth was reported an average of 22.6 minutes after injection. Tests 30 minutes after injection showed a small decrease (0.42 seconds) in speed to run 100 yards on level ground. Ketchum et al. (1973a) reported drowsiness 30 to 60 minutes after injection of atropine sulfate. One group of subjects received 75 ug of atropine sulfate per kg of body weight (about 5 to 6 mg for the average subject) given intramuscularly. This group repeatedly took a number facility (NF) test as a measure of CNS disturbance (Moran and Meffered, 1959). The performance of these subjects fell to 90 percent of baseline performance during the first hour after injection. Mean test scores were depressed below this level for 1 to 7 hours after injection. Mean test scores bottomed out near 80 percent of baseline 4 to 7 hours after injection. This group showed complete recovery 9 hours after injection.

Physiological effects

The body's response to atropine is well described in the literature. In his review of this literature, Headley (1982) found physiological reactions to atropine, when administered to healthy volunteers in normal clinical or doctrinal doses and in the absence of anticholinesterase (organophosphate) challenge, could be expected in heart rate and blood pressure, hydration, temperature, and vision.

Heart rate and blood pressure

The consistency with which atropine increases human heart rate is predictable enough that it has been used as an indicator of rate of absorption and blood concentration of the drug. Kalser and McLain (1970), for example, showed the blood level of radio-labeled atropine administered intramuscularly begins low and rises with time. Heart rate indicated this by falling at first (within 5 minutes) and then rising to a maximum in 30 to 60 minutes. With parenteral atropine doses of 2 to 5 mg, an average heart rate increase of 30 to 50 beats per minute can be expected. Thus, the change in heart rate from the resting, nondrug rate appears to be a good indicator of blood level of atropine. Blood pressure decreases of up to 10 mm Hg in both systolic and diastolic readings have been reported.

Hydration

Resting sweat gland activity and active sweat production are reduced greatly. Urine specific gravity indicates the concentration of urine residing in the bladder and, thus, grossly reflects the overall state of hydration of the serum arriving at

the glomeruli. The levels of specific gravity usually vary widely within the range 1.005 (indicating good hydration) to 1.030 (indicating poor hydration). Values higher than this range indicate potential dehydration, while those lower often indicate episodic fluid intake with transient hemodilution. Thus, urine specific gravities, too, appear to be useful indicators of blood level of atropine.

Body temperature

Atropine's effects on rectal and skin temperature have ranged from absolutely no effect on resting individuals to an increase of 3-4 degrees Centigrade under strenuous working conditions.

Vision

Atropine causes mydriasis and cycloplegia. Subjects may thus experience difficulty in near vision and visual fatigue. Two milligrams of atropine has caused blurred vision for up to 6 hours postinjection, and could, therefore, be of critical concern to aviators. Other visual functions such as threshold and time course of dark adaptation, depth perception, eye muscle balance, and visual field have been undisturbed by atropine at doses of up to 4 mg. The importance of vision to pilots and the individual differences observed justify further elaboration (in the next section).

Ketchum et al. (1973a) used a behavior checklist and symptoms checklist as input to probit analysis to estimate the effective dose for 50 percent of the population (ED50) to produce various side effects. Results were reported in millionths of a gram per kilogram (ug/kg) as given in Table A-2. Since those data are based on a sample population with an average weight of 74 kg, Table A-2 has been expanded to include a right-hand column which gives the equivalent dosage in milligrams for a 70 kg person.

These data imply some recipients will be almost free of behavioral effects when given up to 6 mg. Moylan-Jones (1969) found 2 of 23 subjects who received 6 mg of atropine reported virtually no side effects at that dosage. Since individuals vary in their sensitivity to atropine, some exhibit symptoms more characteristic of a larger dose. For example, Moylan-Jones (1969) reported some degree of visual hallucinations for seven subjects and frank visual and auditory hallucinations for one man.

On the low end of the dosage continuum, Cullumbine, McKee, and Creasey (1955) reported 2 mg was associated with dry mouth and throat (37 of 45 subjects); dizziness, giddiness, light-headedness

(5 of 45 subjects); and difficulty in reading (8 of 45 subjects). Observed physiological effects included the usual findings of

Table A-2.

Effective dose of atropine needed to produce various behavioral effects

Select Items	ED50 (ug/kg)	70 kg man (in mg)
Poor coordination	89	5.2
Short attention span	95	6.6
Eyes blurred	100	7.0
Felt drunk	129	9.0
Confused time	130	9.1
Cannot obey simple requests	135	9.4
Nauseated	146	10.4
Partial amnesia	164	11.5
Hallucinating	169	11.8

Source: Ketchum et al., 1973a.

increased pulse rate and dilation of pupils. Those authors concluded "...there should be no hesitation in administering 2 mg atropine sulfate in all cases of doubt..." concerning nerve gas exposure.

Vision Effects

Some visual functions are not affected by atropine, while others demonstrate effects lasting up to 48 hours. Marzulli and Cope (1950) found no meaningful changes in eye muscle balance, visual field, and night vision. Rubin (1956) confirmed dark adaptation remains unchanged by atropine. Miles (1955) injected 10 volunteers with 2 mg of atropine and measured pupil size and near and distant vision at intervals of 1, 2, 6, 12, and 24 hours. The 3.22 mm mean pupil size before atropine increased to 3.95 and 4.05 mm after 3 and 6 hours, respectively. The measurement taken 12 hours postinjection yielded the maximum figure (4.3 mm). By 24 hours postinjection, the size had reduced to 3.55 mm. The base-line for reading small type was a distance of 73.8 mm; however, within 1 hour after injection, the distance increased to 84.2 mm

and later reached a maximum distance of 100.1 mm (3-hour interval). For the next 9 hours, the figure fluctuated around 99.0 mm. Distant vision remained unchanged throughout the experiment.

Moylan-Jones (1969) reported 23 subjects participating in the performance of routine tasks associated with a military field exercise subjectively rated their recovery between 4 and 48 hours after injection of 6 mg of atropine. Mydriasis, which occurred in all subjects, still was evident in 21 subjects, 48 hours post-injection. Disorders of perception occurred in 10 of those subjects. One man experienced frank visual and auditory hallucinations while seven men experienced visual hallucinations, such as seeing colored flashes of light. Two other men experienced gustatory hallucinations (i.e., fresh water tasted salty).

Cullumbine, McKee, and Creasey (1955) administered intramuscular injections of 2 mg, 3 mg, and 5 mg atropine sulfate to healthy male volunteers. Pupils in all subjects were dilated fully by all three doses of atropine used, but no alteration of near or distant visual acuity could be detected by Snellen Test Charts. After the 5 mg dose, however, all 44 subjects reported difficulty in reading. Approximately one-fourth of the subjects reported difficulty at the 2 and 3 mg levels. These findings generally held true for intramuscular injections, oral doses, and a combination of the two.

The effects of atropine and hyoscine were compared by Mirakhur in 1978. Data regarding pupillary size and near point of vision were obtained for three dosage levels of each drug (0.5, 1.0, and 2.0 mg orally and intramuscularly). According to the author, ocular effects of 2.0 mg atropine intramuscularly were statistically significant from 2 hours onward. Atropine at 0.5 and 1.0 mg also resulted in mydriasis by 3 hours postinjection. Only the 2.0 mg oral dosage achieved any appreciable pupillary dilation and was considered to have produced effects similar to that of 1.0 mg intramuscularly. In each case, near-point vision was affected only minimally, though the most persistent subjective effect was blurring of vision.

A review by Headley (1982) presents a table of the percentage of subjects showing subjective symptoms to atropine. In regard to dosage levels of 2, 3, 4, and 5 mg, reading difficulty consistently increased along with the increased dosage resulting in 39 percent of the subjects experiencing difficulty at 2 mg, and 100 percent of the subjects experiencing difficulty at 5 mg. Photophobia was a complaint of 25 of 286 subjects. Work done by Ketchum et al. (1973a) required the use of eye drops and corrective lenses for subjects to participate in cognitive testing.

Since atropine has marked ocular effects (e.g., mydriasis and cycloplegia) which affect pupil size and accommodation, large effects on the visual contrast sensitivity function, particularly

at the high spatial frequencies (i.e., 2 cpd and above), can be expected. A number of drug studies have documented altered pupil size and/or accommodation and effects on contrast sensitivity. Green and Campbell (1965) found for moderate levels of positive lens defocus (up to +2.5 D) there was no loss in contrast sensitivity at low spatial frequencies; but, for spatial frequencies above 3 cpd, the loss was proportional to lens power. Campbell and Green (1965) assessed the effects of pupil size per se using various artificial pupil sizes under topical atropinization. Using lenses to compensate for accommodative loss and neutral density filters to compensate for the changes in retinal illumination due to the changes in pupil area, they found a progressive reduction of contrast sensitivity as the pupil was made larger.

Kay and Morrison (1985) replicated the Campbell and Green study, except changes in retinal illumination associated with changes in pupil size were not compensated for, in order to simulate natural viewing. In contrast to results of the earlier study, Kay and Morrison found contrast sensitivity was relatively unaffected by pupil diameter. Similar results were obtained by Singh et al. (1981), who found mydriasis alone without paralysis of accommodation did not affect contrast sensitivity in normal older (50 to 84 years) observers. Baker et al. (1983) found, for subjects who had been given atropine intramuscularly, a small loss of sensitivity only at the highest tested spatial frequency (20 cpd).

Bachman and Behar (1987) found the CSF with dilated pupil was reduced significantly, particularly at the spatial frequencies above 2 cpd. When a glare source was added to the viewing conditions, the loss in contrast sensitivity with increased pupil size was markedly increased. The reduction of the CSF by a glare source previously had been demonstrated by Paulsson and Sjostrand (1980), Sturgis and Osgood (1982), Finlay and Wilkinson (1984), and Behar (1984). Carney and Jacobs (1984) stated the CSF can be sensitized by the presence of a glare source to allow a more accurate determination of any visual loss.

Cognitive and information processing effects

Atropine does not seem to produce any permanent effects on cognitive ability. Ketchum et al. (1973a) reported performance of subjects who received 75 ug/kg (about 5.2 mg for 70 kg subject) returned to baseline within 9 hours. Cognitive performance of subjects with higher doses (125 and 175 ug/kg) did not return to baseline within 12 hours, but this may have been a fatigue artifact. Kleininger, Zsadyani, and Molnar (1974) tested subjects before and after atropine coma produced by large doses (2 mg per kg of body weight). Results indicate atropine did not degrade memory or intelligence following recovery.

There are, however, temporary effects at doses as low as 2 mg. Robinson (1953) found inconsistent effects of atropine on a letter matching task. Four of seven subjects showed a decrement in cognitive performance, but mean differences were moderated by a minority of subjects whose performance was stable or improving.

Holland, Kemp, and Wetherell (1978) found cognitive decrements from 2 mg atropine on a NF task, but not on grammatical reasoning. These authors gave tests at 30-minute intervals in order to identify delayed cognitive effects. Marzulli and Cope (1950) tested subjects 1 hour after a single injection of 3 mg of atropine and found no effect on digit recall, arithmetic speed, or reading time.

In their technical report, Ketchum et al. (1973b) provide a regression line relating atropine dosage level to maximum decrement in NF test scores. This linear regression line predicts about a 5 percent decrement from baseline for 2 mg of atropine and less than 20 percent decrement for 4 mg--all assuming an average 70 kg male.

Work with atropine and other anticholinergic drugs in both humans and animals supports the general statement that memory is affected (Weingartner, Sitaram, and Gillin, 1979; Potamianos and Kellett, 1982; Deutsch and Hamburg, 1966). Ketchum et al. (1973a) found remote memory seemed virtually intact, although there was a considerable deficit for experiences of the previous few hours. At higher doses (10-14 mg), many subjects could not even repeat short sentences or number sequences.

Wetherell (1980) had subjects listen to and repeat sequences of random digits lengthened by one-digit steps until errors were made in two consecutive sequences. The test was conducted 60 and 120 minutes after subjects were injected with 2 mg of atropine. Atropine-treated subjects recalled fewer digits than they did before treatment. Wetherell concluded atropine impairs memory function by an effect on information storage rather than a retrieval process.

However, Marzulli and Cope (1950) reported up to 3 mg of atropine did not result in a performance decrement involving a digital recall task. Crow and Grove-White (1973) also found no impairment on a free-recall test after 0.6 mg of atropine.

In general, there is little data concerning the time course of cognitive effects of low dosage levels (2-4 mg) because researchers have tended to give behavioral tests too soon (30-60 minutes after injection). Ketchum et al. (1973a) presented data suggesting cognitive effects reach full effect much later (4-7 hours). These authors provided a description of the subjects' cognitive states that included deficits in time sense and orientation, abstraction, judgment, and speech capability. However,

these cognitive abilities were not tested objectively; and, it is difficult to tie these problems to dosage levels or time course or to generalize to piloting a helicopter.

At a high dosage level, Ketchum et al. (1973a) showed a maximum decline of the group mean to about 80 percent of baseline on the NF test. This period lasted from 4 to 7 hours after injection of 75 ug of atropine per kg of body weight (i.e., 5.25 mg for a 70 kg male). Moylan-Jones (1969) found a lack of immediate atropine effects on the NF test taken within an hour of a 2 mg injection, but a 42 percent decrement several hours after completing a 6 mg set of injections. The differences between the results of Ketchum et al. (1973a) and Moylan-Jones (1969) may be due to a state learning effect. Ketchum et al. repeatedly tested their subjects, thus giving the subjects more opportunity to adjust to test-taking with the internal state produced by atropine.

Attention

Sustained attention has been shown to be under CNS control (Brown and Warburton, 1971). The data of Ketchum et al. (1973a) indicated half the population will develop a shortened attention span with about 7 mg of atropine. The data of Callaway and Band (1958) support the notion that atropine acts to widen the attention span of the subject. It is particularly interesting that Miles (1955) reported 14 errors in the control trials, but only 2 errors in the atropine trials for a discrimination reaction test. It is possible some degree of atropine pretreatment may improve performance on tasks which require divided attention.

Fatigue and sustained operations

Atropine sulfate affects behavior partially through alteration of psychological states. A subjective feeling of fatigue, developing 30 to 60 minutes after injection of atropine, is one of the most commonly reported changes in psychological states (Cullumbine, McKee, and Creasey, 1955; Ketchum et al., 1973b; Moylan-Jones, 1969). Apparently, doses of 2 mg are sufficient to produce this effect.

Safer (1970) used the NF test (Moran and Meffered, 1959) to quantify the effect of one night's sleep loss, an anticholinergic drug (scopolamine), and both treatments combined. The combined effect as measured by the NF test was greater than the effect of sleep loss alone.

Davies and Sargeant (1979) reported evidence there is a direct relationship between oxygen uptake (percent maximum consumption) and ratings of perceived exertion while exercising on a treadmill.

The relationship between heart rate and perceived exertion is less direct. Subjects were given 1.8 mg of atropine and exercised on a treadmill. After 10 minutes of exercise, heart rate was elevated, but oxygen uptake and ratings of perceived exercise were unchanged. The increase in heart rate caused by atropine did not immediately affect the relationship between perceived exertion and oxygen usage. However, after 60 minutes of exercise, subjects treated with atropine reported more perceived effort than those without atropine. Those given atropine did not use more oxygen. In other words, under the influence of a small dose of atropine, subjects reported their effort to be greater than their oxygen usage would warrant.

Psychomotor effects

In reviewing the psychomotor skill area, the authors have avoided the rather large body of literature which demonstrates atropine reduces the willingness and ability to perform heavy labor primarily because of the difficulty in defining "heavy labor" in a helicopter simulator environment. Moylan-Jones (1969) provides an apt summary of the situation:

In the case of manual labor, it seems that the task would either be abandoned or greatly delayed; but, if circumstances such as warfare or an industrially dangerous situation forced the drugged men to continue working hard, heat casualties may be expected, especially if any form of protective clothing is worn.

In terms of whole body movement, Robinson (1953) found 2 mg did not affect obstacle running; but, Cullumbine, McKee, and Creasey (1955) reported 5 mg had an effect of slowing running speed, while 2 mg of atropine did not.

Miles (1955) reported decrements in both visual and auditory reaction times after injection with 2 mg of atropine. Holland, Kemp, and Wetherell (1978) found a similar decrement in a simple reaction time test following a 2 mg injection. The latter decrements were statistically significant at 3.5 and 4 hour following injection with atropine.

Linnoila (1974) reported 0.5 mg of atropine decreased choice reaction time and Miles (1955) found 2 mg of atropine improved discrimination reaction time. In addition, decrements in simple reaction time and improvements in choice reaction time are consistent with findings suggesting a widening of attention due to atropine. (Atropine effects on attention are reviewed in a separate section below.) Holland, Kemp and Wetherell, (1978) did not find any effect upon coordination when administered 2 mg of atropine while performing a pursuit rotor task. Linnoila (1974)

reported no consistent effect on a coordination test following 0.5 mg atropine.

Several studies found no significant degradation of rifle accuracy due to 2 mg or 4 mg of atropine (Cullumbine et al., 1952; Cullumbine, McKee, and Creasey, 1955; Robinson, 1953; and Moylan-Jones (1969) found no effect on accuracy from 6 mg, although the placement of shots was qualitatively different.

Moylan-Jones (1969) employed 6 mg of atropine and found statistically significant decrements in amount of earth dug and in accuracy of a map and compass test. Also, there were trends of taking more time to change a wheel on a vehicle and for a medical team to perform less well. The overall status of skilled psychomotor performance is given an apt qualitative description by Moylan-Jones (1969) as he wrote:

Tasks involving skill, and especially those involving the use of tools or instruments, were performed on the whole more slowly and less efficiently under the influence of atropine, and decisions made by those in charge of others (for example, the medical officer) took longer to make and were sometimes wrong.

Appendix B

List of manufacturers

Apple Computer, Inc
20525 Mariani Avenue
Cupertino, CA 95014

Cadwell Laboratories, Inc
1021 Kellogg Street
Kennewick, WA 99336

Cambridge Instruments, Inc
P.O. Box 123
Buffalo, NY 14240

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

Digital Press (DEC)
12A Esquire Road
Billerica, MA 08162

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 and Co.
307-T East McCarty Street
Indianapolis, IN 46285

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

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

Nicolet Biomedical Instruments
5225-4 Verona Road, P.O. Box 4287
Madison, WI 53711-0287