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<p>Combinations of atropine (up to 4 mg/70 kg) and 2-PAM Cl (up to 1200 mg/70 kg) were studied for their effects on a pursuit tracking task, six visual functions, heart rate and blood pressure, and cognitive functions as measured by six psychological tests. Tracking performance in both bright and dim light was significantly degraded up to 3.5 hr after injection. High- and low-contrast near acuity was significantly altered up to 6 hr after injection, whereas accommodation and pupil size remained altered for 24 hr. Elevated pulse rates were observed for 4 hr. Elevated systolic blood pressures were observed for 2hr. while diastolic pressures remained elevated for 6 hr. No drug effects were found for the psychological tests. Overall, the observed effects of these two drugs in combination are qualitatively similar to those of atropine alone although they are of greater magnitude. On two measures (accommodation and diastolic blood pressure), 2-PAM Cl was found to significantly potentiate the atropine effect. <i>Keywords:</i></p>			
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Combined Atropine and 2-PAM Cl Effects on Tracking Performance and Visual, Physiological, and Psychological Functions

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Combinations of atropine (up to 4 mg · 70 kg⁻¹) and 2-PAM Cl (up to 1 mg · 70 kg⁻¹) were studied for their effects on a pursuit tracking task, six visual functions, heart rate and blood pressure, and cognitive functions as measured by six psychological tests. Tracking performance in both bright light and dim light was significantly degraded up to 3.5 h after injection. High- and low-contrast near acuity was significantly altered up to 6 h after injection, whereas accommodation and pupil size remained altered for 24 h. Elevated pulse rates were observed for 4 h. Elevated systolic blood pressures were observed for 2 h while diastolic pressures remained elevated for 6 h. No drug effects were found for the psychological tests. Overall, the observed effects of these two drugs in combination are qualitatively similar to those of atropine alone although they are of greater magnitude. On two measures (accommodation and diastolic blood pressure), 2-PAM Cl was found to significantly potentiate the atropine effect.

ORGANOPHOSPHATE chemical warfare agents produce their toxic effects by irreversibly binding acetylcholinesterase, the enzyme responsible for hydrolyzing the neurotransmitter acetylcholine into choline

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Human volunteers participated in these studies after giving their free and informed consent. Investigators adhered to AR 70-25 and USAMRDC Reg. 70-25 on the use of volunteers in research. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense (AR 360-5).

and acetic acid. With this enzyme inactivated, excessive concentrations of acetylcholine result in respiratory distress, gastrointestinal symptoms, convulsions, and death. Two complementary methods reverse the effects of excess cholinergic stimulation: a) competitive receptor blockade prevents the binding of unhydrolyzed acetylcholine; and b) the inhibited enzyme is reactivated by freeing it from its organophosphate bonds. Competitive receptor blockade is achieved by atropine and other anticholinergics while enzyme reactivation is accomplished by oxime nucleophilic agents, such as 2-PAM Cl (pyridine-2-aldoxime methyl chloride or pralidoxime) (11,13).

In order to counter the threat of chemical nerve agents, soldiers are issued drug antidotes, which can be self- or buddy-administered if they suspect they have been exposed to a chemical nerve agent or exhibit symptoms. Similarly, atropine and 2-PAM Cl are the standard nerve agent antidotes currently available to Air Force and Navy personnel. Soldiers now carry three sets of atropine and 2-PAM Cl autoinjectors. Each set contains a 2 mg autoinjector of atropine and a 600 mg autoinjector of 2-PAM Cl. Thus, the total possible self-administered dose for each soldier is 6 mg atropine and 1800 mg 2-PAM Cl.

Because of widespread cholinergic innervations throughout the human nervous system, any perturbation of the cholinergic receptors and enzyme functions can be expected to have profound physiological and behavioral consequences. The effects of anticholinergics and cholinesterase reactivators have been studied for many years (4). Over the past 2 years, our laboratories have collaborated in a comprehensive evaluation of atropine and 2-PAM Cl on a variety of functions and tasks. The purpose of our studies was to examine the effects of these two drugs, alone and in combination, on a visual motor tracking task that requires skills similar to those needed to operate many Army systems, to measure changes in vision and visual functions, to docu-

ment the physiological changes in heart rate and blood pressure, and to analyze the effects these drugs have on a number of cognitive functions and psychological measures. We have attempted to perform an encompassing set of studies where many tasks and functions of general medical interest and military relevance are examined together. As aviation skills presume excellent vision and unimpaired visual functions, results in those sections will be of particular interest to aviation specialists. We have reported recently the separate effects of atropine and 2-PAM Cl on performance and visual functions (3,7). We now report their combined effects on performance and vision and additionally on a psychological test battery.

MATERIALS AND METHODS

Ten male civilian volunteers (range 22–33 years) participated in a Latin square experiment using saline placebo, 2 and 4 mg atropine $\cdot 70 \text{ kg}^{-1}$ of body weight, and 600 and 1200 mg 2-PAM Cl $\cdot 70 \text{ kg}^{-1}$ of body weight. Although before the injections neither experimenter nor volunteer knew the drug(s) or dose(s) of that day, the readily discernible side effects of the drugs (atropine's dry mouth and 2-PAM Cl's pain at the injection site) quickly alerted the volunteer that he had received either or both drugs. Serving as his own control, each volunteer received all nine possible injection conditions. Drugs were given by separate injections intramuscularly in the thigh. Injection days were scheduled no closer than 72 h to allow for complete clearance of the drugs and to prevent possible tolerance or carry-over effects. Results were analyzed by the nonparametric Walsh Test (10). The Walsh test compares each individual against his own baseline score and then submits these differences to statistical analysis. Significance level was set at $p < 0.05$. Results report the comparisons of a particular drug group with placebo or the comparison between two drug groups.

Tracking: On each day, volunteers performed three sets of a pursuit tracking task: at preinjection or baseline control, and at 1 h and 3.5 h after injection. Pursuit tracking was performed within a simulated field bunker using a laboratory-constructed, viscous-damped optical device that simulated various Army weapons systems (7). Each set of tracking consisted of 20 15-s tracking trials. Half were conducted under daylight conditions, and half were conducted under dusk/dawn conditions. Volunteers were required to track a tank operating on a rolling course at a simulated distance of 1.2 km and traveling at 5 milliradians per second ($\text{mrad} \cdot \text{s}^{-1}$)-equivalent to 20 mph.

Visual Functions: Measurements were taken for: 1) Near (40 cm) and distance (20 ft) acuity for both high (90%) and low (10%) contrast using standard Bailey-Lovie charts; 2) Accommodative amplitude in the primary (straight ahead), upgaze (45°), and downgaze (45°); 3) Pupil size; 4) Color discrimination with desaturated D-15 color cup ranking test; and 5) Stereopsis by means of the Randot test viewed at 40 cm. These tests were administered at 30 min before injections and at 1.5, 3.5, 6.75, 24, and 48 h after injection.

Physiological Measures: Pulse rates and systolic and diastolic blood pressures were taken 90 min prior to

injection, at 13 times during the day after injection up to 6 h, and at the 1 day and 2 day followup. Volunteers also recorded a subjective rating of pain at the injection site and a "high" rating to the psychoactive effects of the drugs. These ratings were taken 60 min prior to injection, five times after injection (15, 30, 45 min, 3 and 6 h), and on the two followup days. In addition, volunteers rated themselves—on a 16-item subjective checklist—at 1.75, 3 and 5.75 h after injection.

Psychological Tests: Several standard and widely used psychological tests were employed to determine if there were cognitive changes following administration of these antidotes. Tests used were: 1) Stroop color-word form test (administered before injection and four times after injection); 2) Five-item acquisition and recall (administered three times after injection); 3) Forward and backward digit span (administered once after injection); 4) Short story acquisition and recall (administered three times after injection); 5) Controlled oral word association (administered once after injection); and 6) Paced auditory serial addition test (administered once after injection).

RESULTS

For ease of presentation and clarity, the figures present the results of 4 mg atropine $\cdot 70 \text{ kg}^{-1}$, 1200 mg 2-PAM Cl $\cdot 70 \text{ kg}^{-1}$, and the combination of these doses vs. the saline placebo condition. The discussion too is limited to these four conditions except where significant effects or important trends were observed with the remaining drug conditions.

Tracking: The vertical and horizontal (lead/lag) components of the tracking task were analyzed as the standard deviation of the absolute angular tracking error expressed in milliradians. This is a measure of variability around a center aiming point and can be thought of as a measure of operator steadiness.

For the horizontal scores, tracking efficiency under daylight conditions was significantly degraded at both times after injection by both 4 mg atropine $\cdot 70 \text{ kg}^{-1}$ alone and its combination with 1200 mg 2-PAM Cl $\cdot 70 \text{ kg}^{-1}$ (Fig. 1). Average standard deviation tracking errors increased to a maximum of about 1.5 times baseline for the combination dose at 3.5 h after injection. Overall, tracking performance was significantly worse under dim light vs. daylight, and greater drug effects were observed under dim light. Significant drug effects were observed for both atropine alone and atropine in combination with 2-PAM Cl at 1 h after injection. Performance remained significantly affected at 3.5 h after injection.

Drug effects on the vertical tracking errors are shown also in Fig. 1. The decreased efficiency in tracking was significant only at 3.5 h after injections of atropine and atropine plus 2-PAM Cl under dim light. Note the differences in the ordinate scale used in this figure. Vertical errors were much less than the horizontal errors overall.

Another method of describing tracking performance is percent time on target. In our studies, we define the central portion of the tank (0.5 mrad square) as the target. (Overall, the tank subtended a visual angle of 4 mrad). This can be thought of as the catastrophic kill

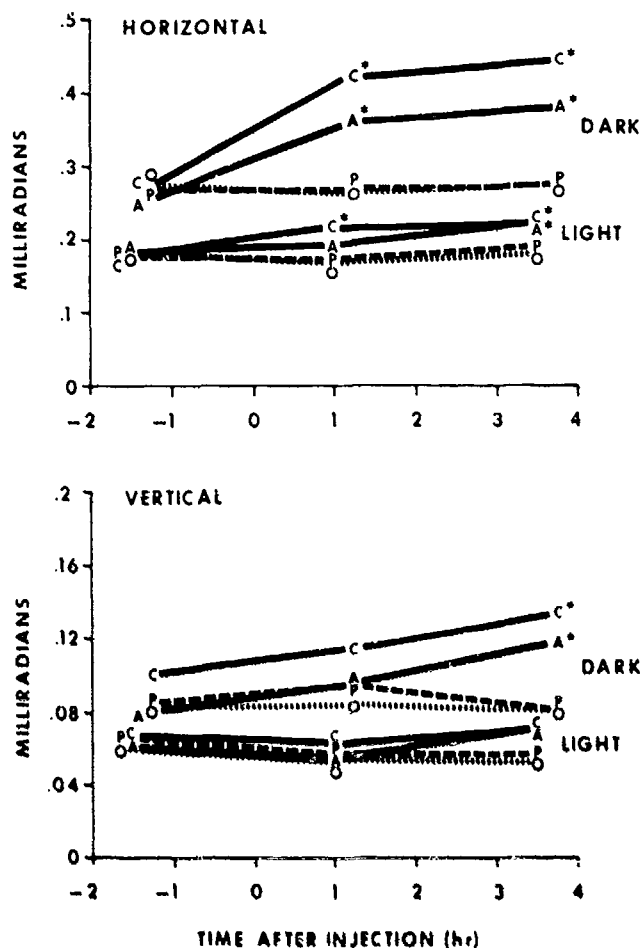


Fig. 1. Time course of the mean standard deviations of the absolute tracking error (N = 10). Note the difference in ordinate scales for the horizontal and vertical scores. The tracking task was largely horizontal in nature and errors were larger in this dimension. Legend: O = Placebo; A = 4 mg atropine · 70 kg⁻¹; P = 1200 mg 2-PAM Cl · 70 kg⁻¹; C = Combination of atropine and 2-PAM Cl; *—Significantly different from placebo, p < 0.05; **—Significantly different from placebo and atropine, p < 0.05.

zone; i.e., a hit here would destroy the tank, not just disable it. The results show decreasing efficiency after 4 mg atropine · 70 kg⁻¹ and the combination dose as time after injection increases (Fig. 2). Significant decreases were observed at 3.5 h after injection in both the light and dim conditions for both atropine alone and in combination with 2-PAM Cl. Additionally, the combination dose significantly decreased percent time on target 1 h after injection in the dim light.

The previous atropine study (7) sampled tracking proficiency at 30 and 150 min after injection. From that study and the atropine alone data in the present study, a more complete time course of the drug's effects can be plotted (Fig. 3). It is evident from these graphs that the point of maximum tracking degradation occurs 2-3 h following a 4 mg · 70 kg⁻¹ dose, with recovery evident at 3.5 h. Tracking ability is affected earlier in the dim light (40% vs. 8% change in the bright light at 1 h), but the maximum percent decrease in efficiency is similar for both lighting conditions (75% change at 2.5 h after injection).

In summary, 2-PAM Cl alone had no effect on tracking performance, while 2 mg atropine · 70 kg⁻¹ did not significantly degrade performance. Efficiency was sig-

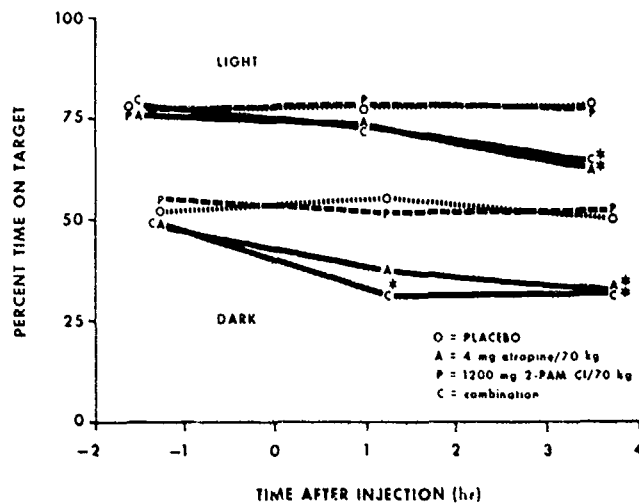


Fig. 2. Time course of mean percent time on target (N = 10). The target was defined as the 1/2 mrad square central portion of the tank.

nificantly affected after the 4 mg · 70 kg⁻¹ dose. The combination of atropine and 2-PAM Cl is statistically the same as atropine alone, although performance is slightly worse, suggesting a synergistic relationship with these two drugs at the highest doses tested. These drug effects reach a maximum at approximately 2.5 h after injection, with some recovery evident at 3.5 h after injection. By testing tracking at times different from the previous study, we now have described atropine's time course more completely.

Visual Functions:

a) *Distance Acuity*—The time course of drug effects shows that atropine alone and in combination with 2-PAM Cl produces small and nonsignificant changes in distance acuity, amounting to about a line on the chart (from 20/16 to 20/20).

b) *Near Acuity*—Fig. 4 shows significant changes in high-contrast acuity after atropine alone and in combination with 2-PAM Cl. The loss of near acuity produced by the combination dose (about four lines on the chart, from the equivalent of 20/12.5 to 20/32) is statistically significant at all three times after injection on the experimental day. Recovery is observed by the following day. The drug-induced changes in low-contrast near acuity are significant up to 6.75 h after injection for both the atropine alone and the combination dose. The maximum change of about 0.4 log minimum angle of resolution corresponds to acuity changes from the equivalent of 20/16.5 to 20/40. The differences between atropine alone and the combination condition are not significant. Alone, 2-PAM Cl produced no changes.

c) *Accommodative Amplitude*—Accommodation was measured as the nearest point of clear vision using a small detailed target. The time course of accommodative amplitude in diopters (D) for the primary gaze is shown in Fig. 5. Substantial (3-4 D) and significant losses were observed at the three test periods after injection for both atropine alone and in combination. Accommodative losses remained significantly affected at the 24 h followup (1-2 D) while complete recovery was not observed until 48 h after injection. At 3 and 3.45 h after the combination dose, four volunteers had less

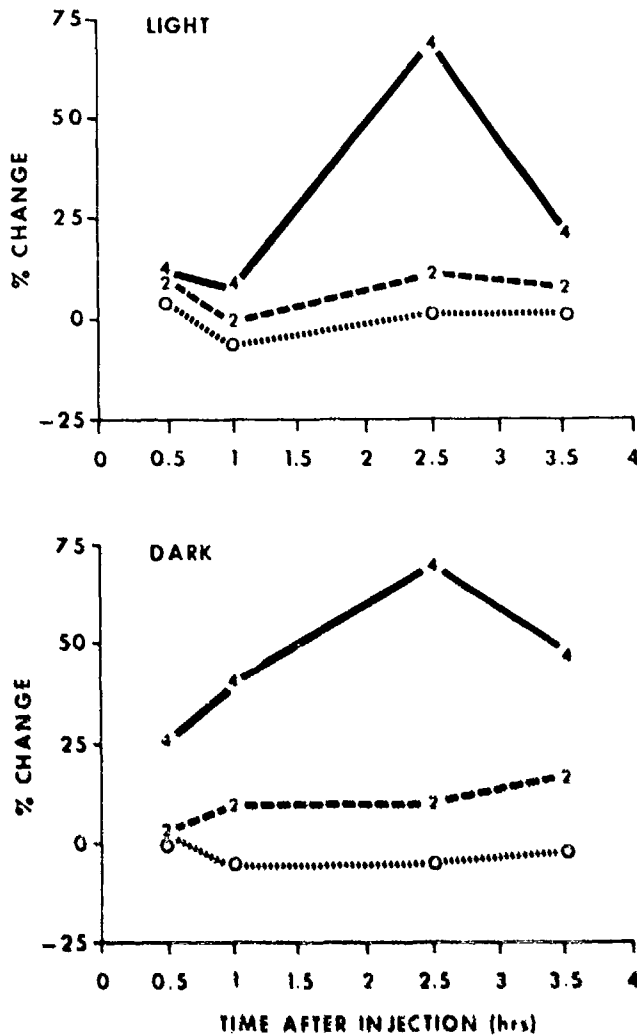


Fig. 3. Time course of mean percent change from baseline of horizontal standard deviations of the tracking error for two doses of atropine (N = 10). Data for 0.5 and 2.5 h are from a previous tracking study (7). Legend: O = Placebo; 2 = 2 mg atropine · 70 kg⁻¹; 4 = 4 mg atropine · 70 kg⁻¹.

than 1 D of accommodative amplitude. Although having no effect by itself, 2-PAM Cl potentiated the 4 mg atropine · 70 kg⁻¹ effect.

There was a clear difference in baseline accommodative amplitude upgaze vs. downgaze (6.5 D vs. 9 D, or 15.4 cm vs. 11.1 cm) verifying the clinical observation that people often need reading additions in the form of bifocals for upgaze before they need it for downgaze. Following the combination dose, accommodative losses for the downgaze were greater than either the primary or the upgaze (6.2 D vs. 4.0 D vs. 4.3 D, respectively).

These losses in accommodative amplitude can be appreciated more, perhaps, when the actual distances in centimeters to the point of near vision are examined. After 4 mg atropine · 70 kg⁻¹ alone, that point was extended on the average by 25 cm. After the combination dose, that distance was extended by 40 cm.

The maximum accommodative loss produced by 4 mg atropine in this study is greater than in our previous study (3). The average maximum loss here was 4.3 D at 4.5 h while the previous study reported a 3.5 D averaged maximum loss at 3.25 h. This discrepancy is due to the

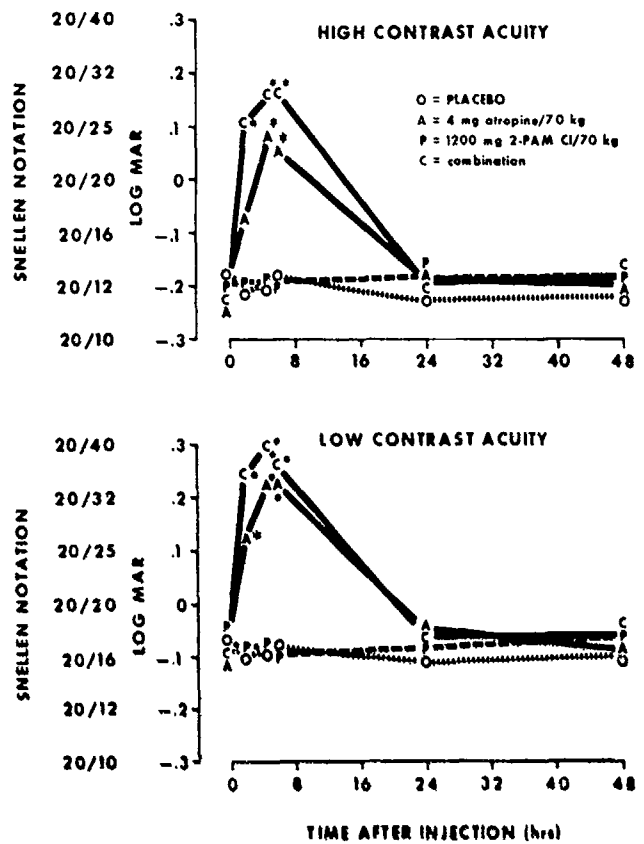


Fig. 4. Mean high (90%) and low (10%) contrast near acuity (40 cm) following drug administrations (N = 10). Ordinate plots both the log minimum angle of resolution measured by the Bailey-Lovie charts and their Snellen notational equivalents.

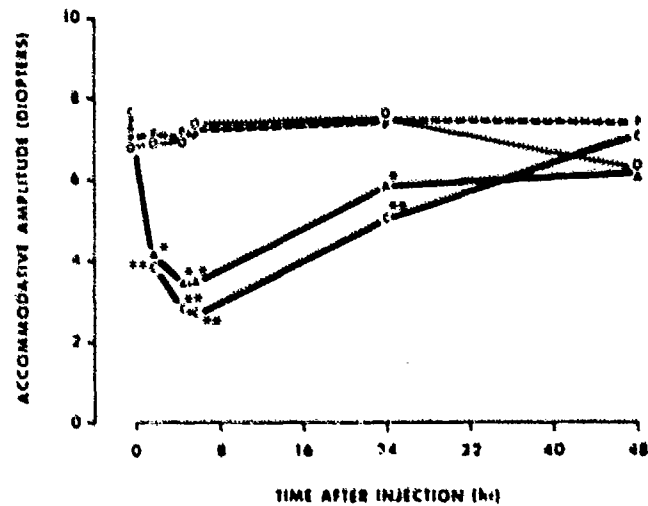


Fig. 5. Time course of mean accommodative loss for the primary gaze following drug administrations (N = 10). Legend as for Fig. 1.

time that the measurements were taken. Accommodative changes are slow, and our previous study apparently did not measure at the point of maximum loss.

d) *Pupil Size and Response*—Pupil size measurements were made using an ophthalmic ruler containing a series of black half circles increasing in 0.5-mm steps. Measurements were made in office room light, a mod-

erate photopic illumination condition of 860 lux. Four milligrams of atropine and its combination with 1200 mg 2-PAM Cl • 70 kg⁻¹ produced significant enlargements at the three measurements made on the injection day (Fig. 6). The changes are small compared to dilations produced by topical mydriatics and are unlikely to be of practical significance in an indoor environment. No significant changes were observed after 2-PAM Cl injections.

A dynamic infrared pupillometer was used with two volunteers. Following the combination of the highest doses of the two drugs, pupil latency and speed of change in response to a penlight stimulus remained unaffected, whereas the amplitude of response decreased from a 2 mm change to a 0.6 mm change. This loss of responsivity to light may be of practical significance, coupled with the cycloplegia observed, since a bright daylight condition can produce dazzle under these conditions.

c) *Color Discrimination*—The desaturated D-15 color vision test (1) was given before and after injection under appropriate lighting (Illuminant C provided by a Macbeth easel lamp). A color confusion index was calculated from the error scores. No significant changes were found in this index after injection, demonstrating that discrimination between pale (desaturated) colors is unaffected by atropine and 2-PAM Cl alone or in combination.

d) *Stereopsis*—The Randot test was given at a distance of 40 cm. This test presents random dot figures visible only using stereopsis as a cue. The disparities are presented through the use of Polaroid filters. At this distance, the smallest disparity is 20 s. Changes observed 4.5 h after the highest combination dose were significant. The loss of stereopsis was very pronounced in three volunteers, who lost all ability to perform the test. The reason for the loss of stereopsis was blur caused by the volunteers' inability to accommodate sufficiently to resolve the detail in the disparity targets. No changes in ocular alignment were observed.

g) *Summary*—Atropine's primary action on the eye of mydriasis and cycloplegia has been shown here to pro-

duce significant and long-lasting effects on near vision acuity, accommodation, pupil size and function, and stereopsis. Atropine's persisting effects observed here are in contrast to clinical mydriatics and cycloplegics, where visual functions recover within 2–4 h. This is due likely to the different routes of administration (intramuscular vs. topical). Although we report no new or unexpected ocular effects of atropine and 2-PAM Cl, the magnitude, time course, and possible synergistic effects are described here in detail for the first time.

Physiological Measures:

a) *Pulse Rate*—Changes in pulse rates after the highest dose of 2-PAM Cl were the same as after saline (Fig. 7). Pulse rates showed a rapid rise after atropine injections. Four milligrams increased rates from an averaged baseline of 70 beats per minute (bpm) to a maximum of 98 bpm at 70 min after injection. The combination of atropine with the highest dose of 2-PAM Cl further increased this maximum to 100 bpm. Both the atropine alone and its combination with 2-PAM Cl are significantly different from baseline, but not significantly different from each other. These increases remained significantly elevated at 4 h and were within baseline levels at 6 h.

b) *Systolic Blood Pressure*—Changes in blood pressure following atropine or 2-PAM Cl alone were non-significant (Fig. 8). Their combination, however, produced significance increases at all time points between 45 and 90 min inclusive.

c) *Diastolic Blood Pressure*—Atropine and 2-PAM Cl produced similar increases in diastolic pressures although 2-PAM's effect was slower-acting and not as long-lasting (Fig. 8). When the drugs were combined, diastolic pressures were synergistically increased by an average of almost 30 mm between 1 and 1.5 h and remained significantly elevated at 4 h. The elevation at 6 h was not significant.

d) *"High" Rating*—Atropine is known to produce psychoactive effects (8), although its time course and magnitude have not been previously documented. In this study, volunteers gave a "high" rating to their sub-

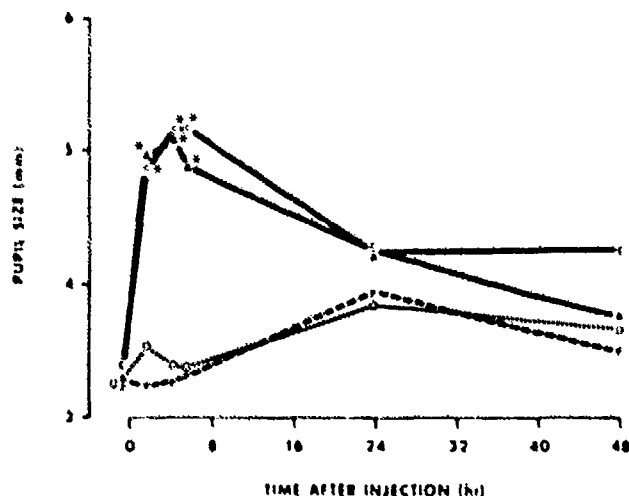


Fig. 6. Time course of mean pupil size following drug administrations (N = 10). Legend as for Fig. 1.

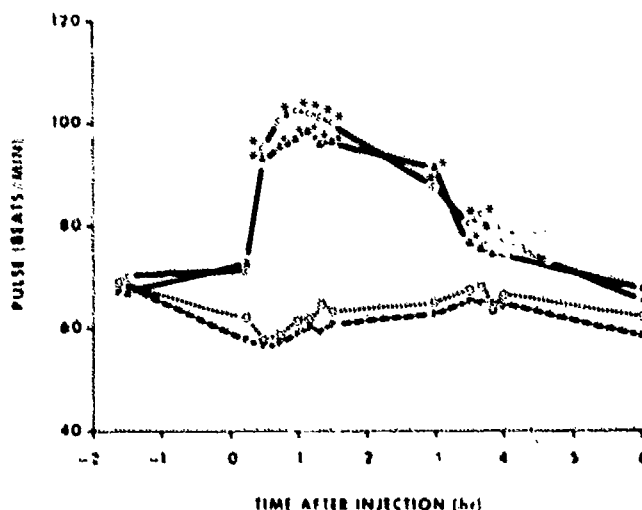


Fig. 7. Time course of mean heart rates during the experimental day following drug administrations (N = 10). Legend as for Fig. 1.

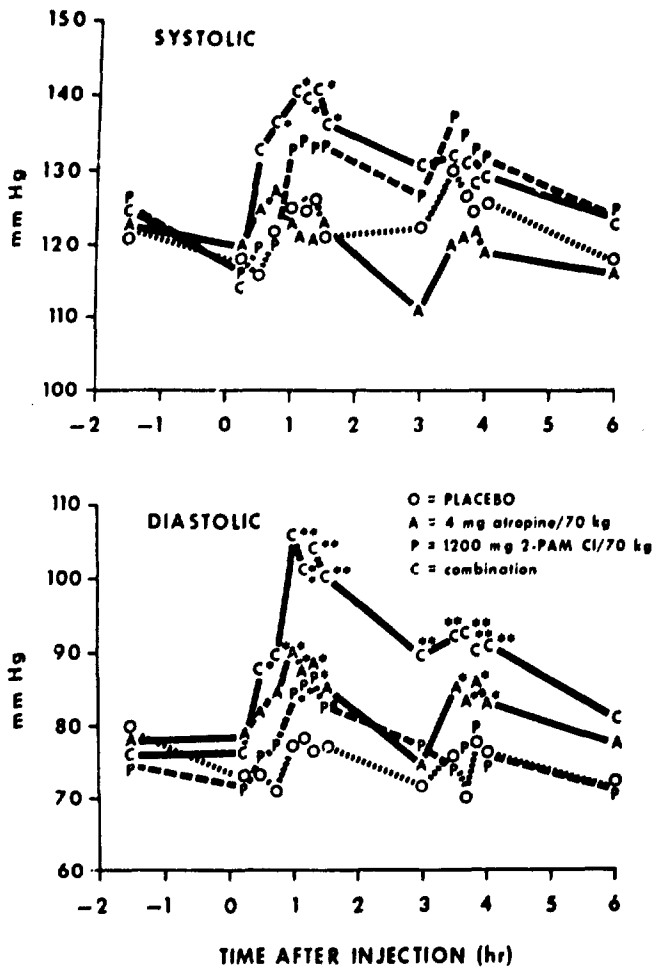


Fig. 8. Time course of mean blood pressures during the experimental day following drug administrations (N = 10).

jective feelings of euphoria on a scale of 0-100, where 100 is the highest they have ever been on any drug. This rating was in addition to the 1-5 "high" rating already on the subjective check list (Table I) which was given at different times. This 0-100 rating closely followed the

cardiovascular effects with rapid onset (15 min) and peaking at 45-60 min. Ratings of up to 25 were recorded following atropine and atropine plus 2-PAM Cl. The rating remained elevated for 3 h. Differences between atropine alone and in combination with 2-PAM Cl were not significant, nor were the slight elevations (ratings of 10 at 15 min) seen after 2-PAM Cl alone. In comparison, the equivalent of two drinks of alcohol produced ratings of 50-60 on this scale (2).

e) *Pain Rating*—Injections of 2-PAM Cl have been reported as painful (12). In this study, volunteers rated the pain at the injection site on a scale of 0-4 (Fig. 9). Atropine and placebo produced negligible effects while 2-PAM alone or in combination significantly elevated the rating for up to 6 h after injection. Some volunteers reported "tenderness" at the injection site 24 h later.

f) *Subjective Sensation Checklist*—Volunteers rated themselves (numerically 1-5) on 16 items (Table I). No significant changes were observed for placebo or 2-PAM Cl alone. Administration of 4 mg atropine • 70 kg⁻¹ and its combination with 1200 mg 2-PAM Cl • 70 kg⁻¹ produced significant increases in ratings of dry mouth, dry skin, and "high" ratings, and significant decreases in distant and near vision at all three times after injection. These ratings returned to normal the following day. Balance and coordination were affected up to 3 h after injection for atropine alone and up to 5.75 h after the combination. All volunteers reported fatigue after the 4 mg atropine • 70 kg⁻¹ dose and significantly reduced concentration after the combination dose up to 4.5 h after injection. The combination dose also caused the subjects to report feelings of restlessness at 1.75 h after injection even though atropine or 2-PAM Cl alone produced no change on this item in these ratings. The remaining sensations of temperature, tension, depression, anxiety, confusion, and forgetfulness were unaltered.

g) *Summary*—The physiological changes observed after atropine injections in this study are consistent with those previously reported throughout the medical and research literature (4). The duration of effect of atropine alone and in combination with 2-PAM Cl is striking and

TABLE I. SUBJECTIVE RATING SHEET.

Mouth	Moist	1	2	3	4	5	Dry
Skin	Moist	1	2	3	4	5	Dry
Distance Vision	Clear	1	2	3	4	5	Blurred
Near Vision	Clear	1	2	3	4	5	Blurred
"High"	Not high	1	2	3	4	5	As high as I have ever been
Temperature	Cold	1	2	Normal	4	5	Hot
Balance	Worse	1	2	Normal	4	5	Better
Coordination	Worse	1	2	Normal	4	5	Better
Tension	Worse	1	2	Normal	4	5	Better
Restlessness	More	1	2	Normal	4	5	Less
Depression	More	1	2	Normal	4	5	Less
Anxiety	Worse	1	2	Normal	4	5	Better
Fatigue	Worse	1	2	Normal	4	5	Better
Concentration	Worse	1	2	Normal	4	5	Better
Confusion	Worse	1	2	Normal	4	5	Better
Forgetfulness	Worse	1	2	Normal	4	5	Better

Volunteers were handed a subjective rating sheet at 1.75, 3, and 5.75 h after injection and asked to circle the number indicating how they felt at that moment.

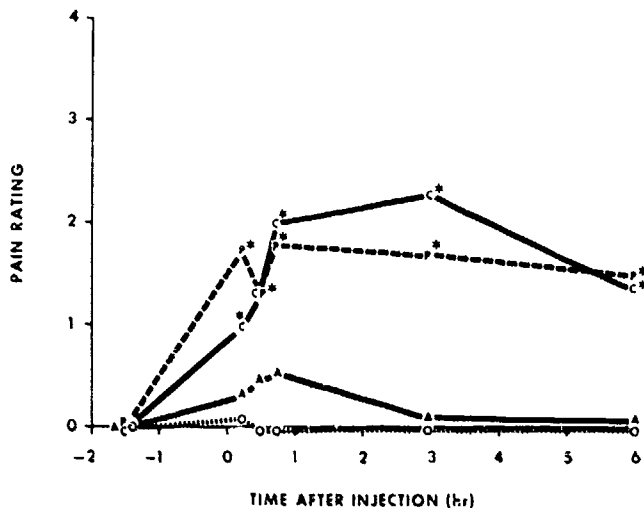


Fig. 9. Time course of mean subjective pain ratings during experimental day following drug administrations (N = 10). Scale was 0=no pain to 4=intense pain. Legend as for Fig. 1.

could be important in the management of emergency medical situations or critical care. The increase in blood pressure, especially diastolic pressure, is of clinical significance in the management of hypertension.

Psychological Tests:

a) *Stroop Color/Word Form Test*—This test measures the ability to inhibit an overlearned response (reading a word naming a color) in order to say aloud the correct color of the printed word. This test is sensitive to diffuse brain dysfunction and frontal lobe dysfunction (5). No significant differences were found for any drug or drug combination. Atropine alone or in combination with 2-PAM Cl did not produce any more or any less interference than placebo at any of the testing times after injection (45 min, 3.5 h, 24 h, 48 h).

b) *Five Item Acquisition and Recall*—Approximately 3 h after injection, a list of five words was read aloud to the volunteer and he was given three chances to repeat the words correctly (immediate recall). No significant differences were found in the ability to acquire or recall (5 min, 24 h, 48 h) after any of the drug doses or combinations at anytime tested.

c) *Forward and Backward Digit Span*—Approximately 3 h after injection, this test of attention span was administered. Volunteers had to repeat digit sets, initially three digits long, and then increasing by one. Testing was continued until an error was made. Sets were repeated forward and then backward. The length of the longest set correctly repeated is the score. No differences in performance from placebo were observed for any drug or drug combination.

d) *Short Story Acquisition and Recall*—Approximately 3 h after injection, each volunteer listened to a short story consisting of 20 details. Immediately after hearing the story, he had to repeat in his own words as much as he could remember. He was asked to recall the story again in 5 min, at 24 h, and at 48 h. Scores consisted of the total number of details recalled. No significant differences between placebo and any of the drug conditions were observed.

e) *Controlled Oral Word Association*—Volunteers

were given two letters (one at a time) and asked to name as many words as they could that started with that letter within a 60-s time period. This test was administered approximately 3 h after injection and measures the ability to use semantic memory. No significant differences were found.

f) *Paced Auditory Serial Addition Test (PASAT)*—The PASAT is a test of auditory vigilance not associated with intelligence or mathematical ability. The test is sensitive to concentration problems, such as those produced by sedative drugs (5). Approximately 3 h after injection, volunteers listened to a tape recording of numbers read sequentially with a specific internumber interval. Their task was to add the last two numbers. Four rates of presentation of 60 numbers were tested: one number every 2.4 s, every 2 s, every 1.6 s, and finally every 1.2 s. No significant differences were found.

g) *Summary*—The results indicate that atropine in doses up to $4 \text{ mg} \cdot 70 \text{ kg}^{-1}$ alone and in combination with $1200 \text{ mg} \text{ 2-PAM Cl} \cdot 70 \text{ kg}^{-1}$ has no significant effect on memory or the cognitive functions required by these tests 3 h after injections.

DISCUSSION

We have measured atropine's and 2-PAM Cl's effects on a wide range of tasks and functions relevant to today's military operations. Atropine has been shown to produce effects on vigilance tasks and tasks requiring immediate recall or consolidating newly acquired information into memory (6,9,14). Our psychological test battery was tailored to incorporate several different psychological tests known to be sensitive clinically for assessing these types of cognitive processes (5). From previous studies, one would have predicted drug-induced decrements in the Five Item Acquisition and Recall, the Forward and Backward Digit Span Recall, the Short Story Recall, and the Paced Auditory Serial Addition Test, with little effect on the Stroop and Controlled Oral Word Association tests. We were unable to differentiate drug from placebo using these tests, however. No significant differences among conditions were observed. One possibility for this lack of a significant difference is that the test battery was administered beyond the point of maximal drug effect. Depending on the variable, maximal drug effects were observed in this study at different times. Physiological measures peaked at 60–90 min while ocular changes and visual-motor performances are most affected 2.5–3.5 h after injection. These results agree with previous studies (9,14,15). Wetherell (14) reported short-term memory effects 60–90 min, but not at 120 min, after injection. This further supports the conclusion that we assessed cognitive functions beyond the optimum time. Additionally, as our volunteers were obviously fatigued at the time of the cognitive tests, there is a possibility we were observing an anticholinergic effect on the general state of the individuals, or so-called tonic arousal. Phasic arousal, however, was unaffected 3 h after atropine because, when required to do so, the volunteers were able to concentrate, attend, and recall material.

The results of the tracking task reveals the magnitude

and duration of the antidotes' effects on psychomotor performance. Performance was degraded in terms of accuracy and steadiness, and was more affected as the task became more difficult under dim light. These results suggest caution for military tasks requiring steady, accurate hand-eye coordination in firing antitank weapons systems or flying aircraft. Such tasks can probably be accomplished at the expense of more target misses and decreased ability to perform more complex maneuvers.

The visual changes observed following drug administration, although of less magnitude than observed clinically following topical applications of cycloplegics and mydriatics, are nonetheless profound and long-lasting. Accommodation does not fully recover until sometime between 24 and 48 h. This loss, in addition to the atropine effects on low contrast near acuity, presents problems for tasks such as map reading where contrast is low and acuity requirements are high.

Physiological changes of heart rate and blood pressure have been extensively reported previously (4). Of particular interest to the medical community from our findings is the apparent synergistic rise in diastolic blood pressure following the combination of 2-PAM Cl with atropine. These rises of approximately 30% for 1-2 h and 10-15% for 4 h are tolerable in healthy, young adults. In older service members, however, where pressures already may be elevated or labile due to a variety of reasons, there is cause for careful observation following the use of these drugs.

In summary, we predict few performance decrements or physiological complications from 2-PAM Cl alone or in combination with up to 2 mg atropine $\cdot 70 \text{ kg}^{-1}$; 4 mg atropine alone or in combination with 1200 mg of 2-PAM Cl is the point at which a host of physiological, visual, and visual-motor effects becomes significant in the benign environment of the laboratory. It remains to be seen what effects these drugs will have upon visual-motor performance and cognitive abilities in military operations where soldiers are sleep-deprived, physically exhausted, hungry, thirsty, and subjected to heat or cold stress. A recent study by Williams *et al.* (15) addressed these questions in part. They assessed the effects of 2 mg of atropine alone and in combination with sleep deprivation and physical exercise on tests requiring perceptual functions. Signal detection capabilities were assessed in a visual target recognition paradigm and in an auditory vigilance task. Signal detection was impaired in the visual target recognition 1.5 h after a 2 mg dose. This effect was potentiated by 24 h of sleep deprivation but not by moderate exercise. Through a sophisticated analysis of these and other tests, they concluded that atropine produces a selective impairment of input perceptual functions rather than of output motor functions, such as response selection and execution.

The use of such paradigms is crucial for a full understanding and prediction of performance effects following antidote injections. Our cognitive tests were unable to indicate a drug effect even when volunteers were visibly fatigued and reported a decreased ability to concentrate. The results from Williams *et al.* (15) indicate that more subtle types of cognitive impairments can be expected following atropine use. Injections of both antidotes produced large and prolonged physiological and visual changes. Interaction of these effects on cognitive functions is posed as a critical but unexplored area in the chemical defense field.

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