

USAARL Report No. 92-26



**Performance Effects
of Chemical Warfare Antidotes:
A Perspective**

By

John A. Caldwell, Jr.

Biomedical Applications Research Division

July 1992

Approved for public release; distribution unlimited.

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

Notice

Qualified requesters

Qualified requesters may obtain copies from the Defense Technical Information Center (DTIC), Cameron Station, Alexandria, Virginia 22314. Orders will be expedited if placed through the librarian or other person designated to request documents from DTIC.

Change of address

Organizations receiving reports from the U.S. Army Aeromedical Research Laboratory on automatic mailing lists should confirm correct address when corresponding about laboratory reports.

Disposition

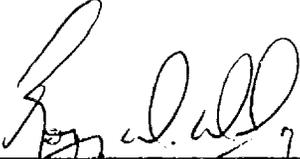
Destroy this document when it is no longer needed. Do not return it to the originator.

Disclaimer

The views, opinions, and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation. Citation of trade names in this report does not constitute an official Department of the Army endorsement or approval of the use of such commercial items.

Reviewed:


for CHARLES A. SALTER
LTC, MS
Director, Biomedical Applications
Research Division


ROGER W. WILEY, O. D., Ph.D.
Chairman, Scientific
Review Committee

Released for publication:


DAVID H. KARNEY
Colonel, MC, SFS
Commanding

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION Unclassified		1b. RESTRICTIVE MARKINGS	
2a. SECURITY CLASSIFICATION AUTHORITY		3. DISTRIBUTION/AVAILABILITY OF REPORT Public Release; Distribution unlimited	
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE			
4. PERFORMING ORGANIZATION REPORT NUMBER(S) USAARL Report No. 92-26		5. MONITORING ORGANIZATION REPORT NUMBER(S)	
6a. NAME OF PERFORMING ORGANIZATION U.S. Army Aeromedical Research Laboratory	6b. OFFICE SYMBOL (if applicable) SGRD-UAB-CS	7a. NAME OF MONITORING ORGANIZATION U.S. Army Medical Research and Development Command	
6c. ADDRESS (City, State, and ZIP Code) P.O. Box 577 Fort Rucker, AL 36362-5292		7b. ADDRESS (City, State, and ZIP Code) Fort Detrick, Frederick, MD 21701-5012	
8a. NAME OF FUNDING/SPONSORING ORGANIZATION	8b. OFFICE SYMBOL (if applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER	
8c. ADDRESS (City, State, and ZIP Code)		10. SOURCE OF FUNDING NUMBERS	
		PROGRAM ELEMENT NO. 0602787A	PROJECT NO. 87A875
		TASK NO. BF	WORK UNIT ACCESSION NO. 385
11. TITLE (Include Security Classification) (U) Performance Effects of Chemical Warfare Antidotes: A Perspective			
12. PERSONAL AUTHOR(S) Caldwell, John A., Jr.			
13a. TYPE OF REPORT	13b. TIME COVERED FROM _____ TO _____	14. DATE OF REPORT (Year, Month, Day) 1992 July	15. PAGE COUNT 12
16. SUPPLEMENTARY NOTATION			
17. COSATI CODES		18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)	
FIELD	GROUP	Atropine (sulfate), Pralidoxime Chloride (2-PAM Chloride), Chemical Defense, Antidotes, Aviator Performance, Military Performance.	
01	02		
05	08		
19. ABSTRACT (Continue on reverse if necessary and identify by block number)			
<p>The threat that enemy forces may use chemical warfare against United States military troops has caused the medical research and development community to find effective antidotes. Particularly in the case of nerve agent poisoning, the timely use of antidote therapies represents the key to survival in contaminated environments. Current training doctrine instructs soldiers how to recognize the symptoms of nerve agent exposure, and then how to counteract the life-threatening effects with the administration of atropine sulfate and pralidoxime chloride. However, these compounds can produce performance degrading effects on their own even when no chemical agent is present. Particularly in the case of the aviator, who is expected to exercise very precise control over an inherently complex vehicle such as a helicopter, the impact of self-administered antidotes should be fully appreciated. The present review briefly summarizes what is known about the actions and performance effects of both atropine and pralidoxime chloride, and recommendations are made concerning the need for additional research.</p>			
20. DISTRIBUTION/AVAILABILITY OF ABSTRACT <input checked="" type="checkbox"/> UNCLASSIFIED/UNLIMITED <input type="checkbox"/> SAME AS RPT. <input type="checkbox"/> DTIC USERS		21. ABSTRACT SECURITY CLASSIFICATION Unclassified	
22a. NAME OF RESPONSIBLE INDIVIDUAL Chief, Scientific Information Center		22b. TELEPHONE (Include Area Code) (205) 255-6907	22c. OFFICE SYMBOL SGRD-UAX-ST

=====
This page intentionally left blank.
=====

Table of contents

Introduction.....	1
Nerve agent threat.....	1
Mechanisms of action.....	1
Symptoms of poisoning.....	2
Countermeasures.....	2
Chemical defense clothing.....	2
Decontamination.....	2
Antidotes.....	3
Supportive care.....	3
Performance effects of antidotes.....	3
Atropine/2-PAM mechanisms of action.....	4
Effects of atropine.....	5
Effects of 2-PAM.....	7
Effects of atropine combined with 2-PAM.....	8
Discussion.....	10
Summary.....	12
References.....	13

=====
This page intentionally left blank.
=====

Introduction

One of the major threats on the modern air-land battlefield is the potential use of nuclear, biological, or chemical (NBC) weapons (Department of the Army, 1989). The NBC capabilities of the Soviet Union and Warsaw Pact countries have been a long standing concern to military tacticians; however, more recently, attention increasingly has been focused upon the potential for use of chemical warfare by Third-World countries such as Iran and Iraq. During the initial stages of Operation Desert Shield, it was reported Iraq was producing more than 1000 tons of nerve agent every year, making Iraq the largest producer of chemical weapons in the Third World (Capaccio, 1990). Thus, it is apparent the NBC threat must be considered a significant and pervasive factor in planning military strategies, regardless of where in the world future conflicts are anticipated.

To effectively minimize the impact of chemical warfare, commanders, aviators, and other soldiers must be aware of the nature of the threat, how and when to use appropriate countermeasures, and the potential effects of both weapons and treatments. The impact of intentional or unintentional misuse of self-administered antidotes should be understood.

Nerve agent threat

Nerve agents are among the deadliest of chemical agents (Departments of the Army, Navy, and Air Force, 1985). They can be delivered by a variety of mechanisms including artillery shells, rockets, bombs, and land mines. These agents are usually colorless and odorless, and they may be either persistent or nonpersistent. Nerve agents are absorbed through any body surface--skin, lungs, eyes, gastrointestinal tract, and membranes of the nose and mouth.

Mechanisms of action

The G-agents (tabun, sarin, and soman) and V-agents (VX) are part of a relatively new class of anticholinesterase compounds, organophosphates, developed during World War II (Taylor, 1985). They affect nervous system functioning by inhibiting acetylcholinesterase at the junctions of cholinergic nerve endings, thus causing acetylcholine accumulation at receptor sites. The primary result is widespread excessive stimulation of cholinergic receptors throughout the body. The toxicity of these

agents stems from both this widespread stimulation and the fact that this effect is persistent.

Symptoms of poisoning

Anticholinesterase agents typically produce stimulation of muscarinic responses, stimulation and subsequent depression of autonomic ganglia and skeletal muscles, and stimulation of cholinergic receptor sites in the CNS (Taylor, 1985). The typical symptoms of toxic effects are constricted pupils, increased sweating and salivation, difficulty in breathing, headache, dizziness, anxiety, cramps, slowed heart rate, and ultimately, convulsions, coma, and death (Mackey, 1982).

Countermeasures

In the event chemical threat environments cannot be avoided, there are basically four components to maximizing survivability on an individual level. Soldiers are trained to respond to chemical exposure by engaging in a specific series of actions.

Chemical defense clothing

Timely donning of chemical protective masks, impermeable clothing, gloves, and boots is essential to survivability in a contaminated environment. Soldiers are instructed to stop breathing and immediately don protective masks whenever agent vapor in the air is suspected (Departments of the Army, Navy, and Air Force, 1985). Aircrews should fly in Mission Oriented Protective Posture status 4 (MOPP-IV) whenever there is a high threat of chemical agent use; however, the wearing of this clothing tends to degrade performance because it limits dexterity, restricts vision and movement, and increases heat stress (Department of the Army, 1989).

Decontamination

In the event of contact between nerve agent and skin, immediate washing of the contaminated area with decontamination pads and/or water will reduce substantially the agent's impact. Use of a decontamination kit such as the M258A1 is the preferred method, but soap and water is the next best method if decontamination kits are unavailable (Department of the Army, 1985b).

Antidotes

If symptoms of organophosphate poisoning become evident, the immediate administration of antidotes is of paramount importance. For this reason, soldiers are trained to recognize the symptoms of poisoning and to administer atropine sulfate and pralidoxime chloride (2-PAM) in a timely fashion (Department of the Army, 1985a). Specifically, soldiers are instructed to inject 2 mg of atropine immediately after the signs of nerve agent poisoning become evident, and to subsequently inject 600 mg of 2-PAM immediately after the atropine. Then, if after 10-15 minutes, symptoms of nerve agent poisoning persist, soldiers are instructed to administer a second set of injections (both atropine and 2-PAM). If after another 10-15 minutes symptoms remain, a third set of injections should be given. Thus, a soldier can self-administer a total of 6 mg atropine and 1800 mg 2-PAM within a 30-minute period.

Supportive care

Following moderate- to high-level exposure to nerve agent, chemical casualties will require respiratory support and anticonvulsant therapy even though they have received substantial nerve agent antidote. Recently, the Army has fielded autoinjectors containing diazepam to reduce the central nervous system damage which results from organophosphate poison-induced convulsions. However, diazepam is not intended for self-administration, and should only be given by another soldier (Department of the Army, 1990).

Performance effects of antidotes

It already has been noted that the wearing of chemical protective clothing may be expected to degrade soldier performance because of restricted vision, reduced freedom of movement, and increased heat stress. Because of these problems, commanders are admonished not to overreact to the NBC threat because the "degradation from [protective clothing] can be as serious as the NBC hazard" (Department of the Army, 1985a). Thus, commanders are placed in the position of having to conduct continuous risk analyses to weigh the potential for chemical attack against the consequences of performance decrements attributable to the chemical defense posture.

Another part of the risk analysis is evaluating the potential for individual soldier's use or misuse of chemical defense antidotes, to include the immediate and long-term impact of self-administered atropine and/or 2-PAM. Headley (1982) says

that antidotes by themselves may have deleterious performance effects, and that antidote misuse on the battlefield is possible due to: 1) uncontaminated soldiers injecting antidotes upon viewing other soldiers (contaminated or not) doing the same; 2) soldiers injecting more antidote than necessary; 3) soldiers injecting antidotes after hearing an alarm, but prior to experiencing symptoms; or 4) soldiers administering antidotes as prophylactics in the belief they will afford protection against an anticipated exposure. Thus, the fielding of individualized chemical first-aid kits introduces the potential for performance problems as a result of inappropriate use.

Unfortunately, most commanders do not possess sufficient information about the potential operational consequences of any of these factors. In addition, even though the field manual on aviation battlefield survivability (Department of the Army, 1989) states "the effects of atropine and 2-PAM on aircrews are being studied," (p. A-16), only part of the questions have been answered to date.

Atropine/2-PAM mechanisms of action

Atropine sulfate is an antimuscarinic agent which is a competitive antagonist of the actions of acetylcholine at receptor sites (Weiner, 1985). Thus, atropine counteracts the impact of organophosphate poisons which exert their effects by increasing the levels of acetylcholine at receptor sites via deactivation of acetylcholinesterase (as previously discussed). Atropine begins to exert an effect within 5-15 minutes of intramuscular injection of a single dose (Kalser and McLain, 1970), with maximal atropine concentration found in expired air at 75 minutes, and maximum atropine concentration in urine at 120 minutes. After 4 hours, 50 percent of atropine is excreted, and after 24 hours, between 87 and 93 percent of the initial dose is excreted into the urine. Unfortunately, while atropine is rapidly effective in blocking the parasympathetic and the central nervous system effects of organophosphate poisons, and while it is quickly eliminated afterward, it is not effective in the relief of the peripheral neuromuscular paralysis which tends to produce respiratory distress.

To counteract these peripheral effects, pralidoxime chloride is required. Pralidoxime chloride is an acetylcholinesterase reactivator which restores the effectiveness of acetylcholinesterase at over a million times the rate of spontaneously occurring hydrolytic regeneration (Taylor, 1985). The 2-PAM can restore motor nerve responses at skeletal neuromuscular junctions within a few minutes after organophosphate poisoning has occurred, and the general autonomic nervous system effects are only limited. There is virtually no

impact of 2-PAM on the CNS. Significant problems related specifically to 2-PAM administration are quite minimal at clinically used dosages of 1 to 2 g.

The time course of 2-PAM administered intramuscularly (up to 10 mg/kg) is shorter than that of atropine sulfate. Sidell and Groff (1971) found plasma levels at therapeutic concentrations within 5-10 minutes with 7.5 and 10 mg/kg doses. Ninety-one percent of 2-PAM was excreted unchanged in the urine within 12 hours, 50 percent was eliminated in the first hour, and 69 percent was eliminated within the first 2.5 hours. Half-life was 75 minutes for the lowest dose tested (2.5 mg/kg) and 83 minutes for the highest dose tested (10 mg/kg).

Effects of atropine

The effects of atropine sulfate on a wide array of physiological, psychological, cognitive, and performance measures have been well documented. Thorough literature reviews may be found in Headley (1982), Simmons et al. (1989), and Caldwell et al. (1992).

The Headley (1982) summary indicates atropine in various dosages (2-6 mg) produces significant vision problems ranging from increased photophobia (increased pupil diameter) to near vision problems such as blurring due to degraded accommodation. In addition, there is elevated heart rate which is maximal about 30 to 60 minutes postdose after a brief period (within 2-6 minutes) of initial slowing, and there is a slight drop in blood pressure. Atropine administration as low as 2 mg has been found to raise body temperature and impair normal evaporative cooling mechanisms--a problem of particular importance when soldiers are wearing protective clothing. There have been subjective complaints of dry mouth, dizziness, drowsiness, and fatigue. Furthermore, although the smaller dose (2 mg) does not appear to be consistently associated with marked behavioral or cognitive changes, there have been decrements reported on overall physical stamina and on reaction time and simple math tests. Four mg was found to impair duties such as night compass exercises and radio operations. To all of these effects, Lobb, Phillips, and Winter (1985) add possible reduced alertness and increased anxiety, with potential impairments in central nervous system functioning.

The effects of 2 mg and 4 mg of unchallenged atropine on the performance of U.S. Army helicopter pilots are discussed in Caldwell, Stephens, and Carter (1991). This in-flight study conducted at the U.S. Army Aeromedical Research Laboratory (USAARL) employed a counterbalanced, within-subjects design in which flight performance, vision, electroencephalographic

activity, cognitive skill, and tracking performance were assessed under placebo, 2 mg atropine, and 4 mg atropine.

The results indicated numerous atropine-related difficulties which were most often associated with the 4-mg dose. Measurements of flight performance revealed decrements in straight and level flight, standard-rate turns, a straight climb and descent, steep turns, a climbing turn, an instrument landing system (ILS) approach, and confined area operations. Vision tests showed increases in pupil diameter and double vision, with decreases in accommodation and near depth perception involving fine detail. Cognitive tests revealed decrements in visual search, logical reasoning, quantitative ability, short-term memory, and choice reaction time. Also, there were increases in psychomotor tracking errors, which were sometimes accompanied by deficits in a secondary task. Electrophysiological data revealed a number of effects on resting EEGs (mainly increased slow-wave activity) which were consistent with the observed atropine-related performance problems.

It was concluded that overall performance under the influence of up to 4 mg of atropine did not appear to be critically impaired (at nontactical, cruising altitudes), but performance close to the ground which required control finesse and accuracy did reveal significant problems. These findings were in general agreement with those of an earlier study on the performance effects of atropine in a rotary-wing simulator (Simmons et al., 1989), which revealed flight accuracy reductions across various parameters of several maneuvers under 4 mg.

In addition, the findings with regard to generalized slowing of the EEG were in agreement with reports made by Longo (1966), who noted substantial reductions of alpha activity (8-12 Hz) particularly under the influence of 4 mg. Such reductions in cortical activation are congruent with the reductions in accuracy and increases in variability of performance observed among many of the experimental tasks. The increased tracking errors across three levels of difficulty on a psychomotor tracking task were in accordance with impairments observed earlier by Penetar and Beatrice (1986), but the USAARL study expanded those findings in terms of further defining the extent and time-course of effects. Specifically, it was seen that tracking decrements were rather pervasive at 4 hours postdose, but most of these psychomotor effects had dissipated by 8-9 hours postdose. The atropine-induced reductions in measures of both the speed and accuracy of cognitive performance were consistent with the decrements predicted by Lobb, Phillips, and Winter (1985); however, it was determined that, particularly beyond 8 hours postdose, some subjects were able to compensate for potential accuracy losses by slowing their performance during the completion of some cognitive subtests.

In general, the USAARL atropine study noted most performance indices were relatively unaffected by 2 mg of atropine, whereas the 4-mg dose caused consistently significant degradations. Also, the investigation revealed aviators may be able to preserve performance accuracy in flight tasks (to some extent) and laboratory tasks when the speed of responses is not critical; however, where response slowing is not an option, performance is often significantly impaired--sometimes to a dangerous extent. One research participant would have crashed during confined-area operations during the in-flight portion of the study if it had not been for timely safety-pilot intervention. Also, the persistence of some performance, EEG, and especially vision effects suggested a minimum of 12 hours would be required prior to returning to flight duty after an unchallenged atropine administration.

Effects of 2-PAM

The well-documented effects of atropine on laboratory tests and especially in-flight aviator performance have been of great interest to the operational community. Although technically speaking, aviators would not administer atropine except after certain exposure to nerve agent, both they and their commanders seem more "comfortable" with the drug because of an understanding of atropine's effects. However, when aviators are presented with findings about the impact of atropine on helicopter pilot performance, they invariably ask about the effects of 2-PAM since, according to doctrine, atropine and 2-PAM would be administered together.

Headley (1982) has summarized the available literature concerning the effects of 2-PAM administered by itself. The data indicate that injections of 2.5, 5.0, 7.5, and 10.0 mg/kg, and oral administrations of up to 8 grams 2-PAM do not produce significant changes in heart rate or blood pressure. There are no signs of toxicity attributable to 1-2 g doses given every 6 hours over a 3-day period, or attributable to doses ranging up to 4 g given daily for a period of several weeks. However, some subjects have reported one or more of the following symptoms: a hot feeling in the facial area, impaired concentration, headache "around the eyes," and/or short-term dizziness. Investigations into the effects of 6 g 2-PAM (in sustained-released tablets) on personnel exercising under various temperature conditions (19, 29, and 46 degrees centigrade) revealed no impact on heart rate, body temperature, sweat rate, or blood pressure. These results were substantiated in a study examining resting subjects given 600 mg 2-PAM in a 40°C environment--heart rate, sweat rate, and skin and rectal temperature were unaffected (summarized by Headley, 1982).

Actually, the only problem consistently associated with acute 2-PAM administration appears to be the occurrence of pain at the injection site. Headley (1982) reported that two investigations (Sidell and Groff, 1971; Vojvodic and Boskovic, 1974) found 2-PAM-related pain, and one of these quantified the level of pain to have been "moderate" at the time of injection and "mild" at 3.5 hours postdose.

The problem with postinjection pain also was reported by Haegerstrom-Portnoy et al. (1987), where it was found subjects experienced pain severe enough to interfere with mental concentration. These authors examined the effects of placebo, 600 mg 2-PAM, and 1200 mg 2-PAM on pulse rate, blood pressure, subjective feelings, visual acuity, pupil size, accommodation, contrast sensitivity, color vision, intraocular pressure, and psychomotor tracking. Physiological measures were taken at baseline, 75 and 195 minutes postinjection; vision measures were collected at baseline, 75 and 195 minutes, and 22 and 46 hours postdose; and tracking was assessed at baseline, 30 and 150 minutes postinjection. Results indicated no significant changes in any of the collected measures at any time after either dose of 2-PAM, with the exception of a small, but significant increase in systolic blood pressure 195 minutes after 1200 mg. Subjective pain ratings at the injection site were, however, increased significantly by both doses of 2-PAM. These ratings returned to baseline levels by 22 hours postinjection.

Effects of atropine combined with 2-PAM

Understanding the impact of atropine sulfate alone or 2-PAM alone answers only part of the question about the potential operational consequences of antidote administration. While 2-PAM appears to be a rather innocuous drug, the possibility exists that 2-PAM in combination with atropine may produce synergistic effects that might be cause for concern. A thorough literature search, however, indicates that little progress has been made toward fully understanding what these effects may be.

Kobrick, Johnson, and McMenemy (1989) have studied the impact of the lower doses of atropine (2 mg) and 2-PAM (600 mg) on visual performance in a hot environment. Subjects completed three test sessions (30, 150, and 270 minutes postdose) per day under placebo, drug (atropine/2-PAM) only, heat (95°F/60 percent relative humidity) only, and drug combined with heat. Results showed drug-related reductions in acuity and far lateral phoria, but stereopsis and contrast sensitivity were unaffected. Heat exposure caused no significant changes, and drug by heat interactions were only minimal (phorias were affected). A second phase of this study was conducted with subjects wearing MOPP IV under essentially the conditions outlined above. Results

indicated visual acuity again was affected by atropine/2-PAM, but also degraded by heat. Phorias and stereopsis were influenced primarily by heat exposure, but there was a slight drug effect in contrast sensitivity. The authors summarized these results by reporting heat stress appeared to be the overall impairing factor, but drug effects on a couple of the vision measures were marked as well. The significant drug effects were considered to be primarily a result of atropine, with little or no contribution from 2-PAM.

Penetar, Haegerstrom-Portnoy, and Jones (1988) studied the impact of two dosage levels of atropine and 2-PAM on tracking, vision, physiological, and psychological variables. The design of the investigation offered information about both separate and combined effects of the two drugs as there were nine experimental conditions (placebo, 2 mg atropine, 4 mg atropine, 600 mg 2-PAM, 1200 mg 2-PAM, and the four atropine/2-PAM combinations). Tracking was measured at baseline, 1, and 3.5 hours postinjection; acuity, accommodation, pupil size, and color vision were measured at baseline, 1, 3.5, 6.75, 24, and 48 hours postdose; blood pressure was measured 13 times postinjection (and during the 2 days afterwards); subjective ratings of injection pain were measured 15, 30, and 45 minutes, 3 and 6 hours, and the next 2 days postdose; and Stroop color-word test, 5-item acquisition and recall, digit span, word association, and auditory serial addition were measured 1-3 times postinjection. The results were as follows:

Tracking performance. Pralidoxime chloride (1200 mg) alone had no effect, while 4 mg atropine and 4 mg atropine in combination with 1200 mg 2-PAM caused significant decrements. Also, while the combination exerted effects quite similar to those of atropine alone, performance tended to be worse with the combination dose, suggesting synergistic effects.

Vision. Distance acuity was unaffected by any dose, but near acuity was impaired by 4 mg atropine and 4 mg atropine in combination with 1200 mg 2-PAM (for 24 hours under high contrast and 6.75 hours under low contrast). Accommodative amplitude also was impaired (through 24 hours) by 4 mg atropine alone and 4 mg atropine combined with 1200 mg 2-PAM--the 2-PAM also significantly potentiated the effects of 4 mg atropine (4 diopters with atropine, 2.5 diopters with the combination). Pupil size was enlarged substantially by 4 mg atropine and 4 mg atropine combined with 1200 mg 2-PAM. Color vision was unaffected by any dose, and stereopsis was impaired at 4.5 hours after the highest combination dose.

Physiological measures. Pulse rate was unchanged by 2-PAM alone, but significantly increased by atropine alone and in combination with 2-PAM (up to 4 hours postdose). Systolic blood

pressure changed under 4 mg atropine and 4 mg atropine combined with 1200 mg 2-PAM, and diastolic blood pressure was increased by each dose separately, although the effect of 2-PAM was slower, and in combination, there was a significant synergistic effect (30 mm Hg increase).

Psychological measures. Subjective euphoria was significant under atropine and atropine in combination with 2-PAM at 15 minutes postdose and remained for 3 hours. Pain ratings were negligible after atropine or placebo, but 2-PAM alone or in combination caused significant elevations for up to 6 hours postinjection. Subjective discomfort in terms of dry mouth, dry skin, balance problems, and fatigue was increased after 4 mg atropine alone or in combination with 1200 mg 2-PAM, but only the combination dose produced feelings of restlessness at 1.75 hours postdose.

Cognitive tests. None of the tests designed to assess memory or cognitive functions revealed changes attributable to any dose administered in this study.

Penetar, Haegerstrom-Portnoy, and Jones (1988) summarized their findings by saying there would be few problems from either 2-PAM alone or 2 mg of atropine, but 4 mg of atropine alone or in combination with 1200 mg 2-PAM would create "a host of physiological, visual, and visual-motor effects" (p. 1132) which probably will be exacerbated by the operational environment.

Discussion

As discussed here, nerve agents are among the deadliest of chemicals which may be used by an enemy against U.S. troops. The currently available agents are both powerful and persistent, and recent experience in Southwest Asia shows that even Third World nations are capable of producing and using these chemicals in military conflicts.

Effective countermeasures include the use of chemical protective clothing, decontamination, and antidote administration. Each of these interventions can be life saving in a contaminated environment, but the use of protective clothing and the administration of antidotes have performance degrading effects on their own. The donning of chemical protective clothing tends to decrease mobility and increase discomfort and heat stress. Antidotes affect visual, cognitive, psychomotor, and physiological parameters of soldiers. In both cases, performance is compromised to various degrees, and commanders must consider the risks associated with these compromises in comparison to the probability of chemical exposure. Especially in the case of helicopter pilots, even modest performance

impairments can be expected to produce serious operational problems.

On the one hand, the work summarized by Headley (1982) and Lobb, Phillips, and Winter (1985) indicates a number of atropine-related effects which will interfere with vision, cognitive skill, and performance. On the other hand, reports by both Headley (1982) and Haegerstrom-Portnoy et al. (1987) suggest pralidoxime chloride by itself appears to have only minimal disturbing effects (other than postinjection pain). The studies examining the combined effects of atropine and 2-PAM (Kobrick, Johnson, and McMenemy, 1989; Penetar, Haegerstrom-Portnoy, and Jones, 1988) raise questions about the types of problems which may result from synergistic drug effects. However, it seems the impact of combined atropine/2-PAM on most operationally-relevant tasks will be minimal. Unfortunately, studies addressing this issue (synergistic effects) in aviators have yet to be accomplished.

There is an extensive database of information concerning the performance effects of both heat stress and atropine in aviator-specific tasks, but information about 2-PAM in this context is lacking. The U.S. Army Aeromedical Research Laboratory has examined the effects of heat stress and chemical protective clothing on aviator performance in a UH-60 simulator (Thornton et al., 1992a); the effects of heat stress, protective clothing, and individual (microclimate) cooling on simulated flight performance (Thornton et al., 1992b); and the impact of 2 mg and 4 mg of atropine sulfate on aviator performance during both simulated and actual flights in a UH-1 (Simmons et al., 1989; Caldwell et al., 1991). All of these have been completed recently, and each study indicates the chemical warfare countermeasures necessary to preserve life in a contaminated environment are themselves not completely free of performance side effects. For instance, it is now known that 4 mg of unchallenged atropine can produce dangerous flight performance decrements in some aviators.

The current base of knowledge certainly has benefited soldiers, pilots, and commanders in terms of describing previously unknown ramifications of chemical defense doctrine. However, additional work remains. As mentioned earlier, there have been no aviation studies on pralidoxime chloride combined with atropine. Also, the effects of 6 mg of atropine and the effects of pretreatment with pyridostigmine followed by administration of pralidoxime chloride and atropine have not been determined. Furthermore, there is a need to understand the extent to which heat problems, sleep deprivation, and ultimately the psychological stress of operating under the threat of chemical exposure will contribute to the side effects caused by existing therapeutic compounds. As Ursano (1988) points out, there is no doubt a profound and complex interrelationship among

all of the biopsychosocial stressors associated with operating in a chemically contaminated environment. Only after these issues are addressed within the framework of empirical research on militarily-relevant tasks can the operational community feel thoroughly informed about the chemical defense decisions they may be called upon to make in the future.

Summary

Currently available chemical warfare countermeasures are of paramount importance for saving lives in a chemically contaminated environment. The published Army doctrine reflects a reasonable and efficacious approach to avoiding and/or treating nerve agent exposure on the battlefield, and adherence to this doctrine should be carefully taught and utilized wherever necessary. However, soldiers, pilots, and commanders must be aware that chemical protection often is associated with performance costs of its own. Protective clothing can increase heat stress and reduce endurance. Antidotes affect central and peripheral nervous system functioning, and this produces visual, cognitive, psychomotor, and physiological changes. Both strategies can be expected to compromise performance to some extent and the operational community should fully appreciate both the costs and benefits of each countermeasure. There is already a substantial database of information which can be used for informational purposes, and part of this database was described here. However, additional work remains if a complete understanding of therapeutic side effects is to be accomplished.

References

- Caldwell, J. A., Carter, D. J., Stephens, R. L., Stone, L. W., Delrie, D. M., Pearson, J., and Simmons, R. R. 1991. Effects of the chemical defense antidote atropine sulfate on helicopter pilot performance: An in-flight study. Fort Rucker, AL: USAARL technical report no. 91-17.
- Caldwell, J. A., Stephens, R. L., Carter, D. J., and Jones, H. D. 1992. The effects of 2 mg and 4 mg atropine sulfate on the performance of U.S. Army helicopter pilots. Aviation, space, and environmental medicine, in press.
- Capaccio, T. 1990. Iraq is a major producer of chemical weapons. Defense week. August 13, 1990.
- Department of the Army. 1985a. NBC protection. Washington, DC: U.S. Army field manual, FM 3-4.
- Department of the Army. 1985b. NBC decontamination. Washington, DC: U.S. Army field manual, FM 3-5.
- Department of the Army. 1988. First aid for soldiers. Washington, DC: U.S. Army field manual, FM 21-11.
- Department of the Army. 1989. Aviation battlefield survivability. Washington, DC: U.S. Army field manual, FM 1-101.
- Department of the Army. 1990. Memorandum HSHA-TLD, Subject: convulsant antidote for nerve agents. Fort Sam Houston, TX: Academy of Health Sciences, U.S. Army.
- Departments of the Army, Navy, and Air Force. 1985. Treatment of chemical agent casualties and conventional military chemical injuries. Washington, DC: U.S. Army training manual, TM 8-285.
- Haegerstrom-Portnoy, O. D., Jones, R., Adams, A. J., and Jampolsky, A. 1987. Effects of atropine and 2-pam chloride on vision and performance in humans. Aviation, space, and environmental medicine. 58: 47-53.
- Headley, D. B. 1982. Effects of atropine sulfate and pralidoxime chloride on visual, physiological, performance, subjective, and cognitive variables in man: A review. Military medicine. 147: 122-132.
- Kalser, S. C., and McLain, P. L. 1970. Atropine metabolism in man. Clinical pharmacology and therapeutics. 11: 214-227.

- Kobrick, J. L., Johnson, R. F., and McMenemy, D. J. 1989. Effects of atropine/2-PAM chloride, heat, and chemical protective clothing on visual performance. Natick, MA: U.S. Army Research Institute of Environmental Medicine. USARIEM technical report no. M36-89.
- Lobb, M. L., Phillips, J. D., and Winter, A. S. 1985. Effects of atropine sulfate on aircrew performance. Arlington, TX: Department of Psychology, University of Texas at Arlington. Technical report no. 85-48.
- Longo, V. G. 1966. Behavioral and electroencephalographic effects of atropine and related compounds. Pharmacological reviews. 18: 965.
- Mackey, C. L. 1982. Anticholinesterase insecticide poisoning. Heart and lung, 11: 479-484.
- Penetar, D. M., and Beatrice, E. S. 1986. Effects of atropine on human pursuit tracking performance. Aviation, space, and environmental medicine. 57: 654-658.
- Penetar, D. M., Haegerstrom-Portnoy, G., and Jones, R. T. 1988. Combined atropine and 2-PAM Cl effects on tracking performance and visual, physiological, and psychological functions. Aviation, space, and environmental medicine. 59: 1125-1132.
- Sidell, F. R., and Groff, W. A. 1971. Intramuscular and intravenous administration of small doses of 2-Pyridinium Aldoxime Methochloride to man. Journal of pharmaceutical sciences, 60(8):1224-1228.
- Simmons, R. R., Caldwell, J. A., Stephens, R. L., Stone, L. W., Carter, D. J., Behar, I., Mitchell, G. W., Knox, F. S., Jones, H. D., and Taylor, P. L. 1989. Effects of the chemical defense antidote atropine sulfate on helicopter pilot performance: A simulator study. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory. USAARL report no. 89-17.
- Taylor, P. 1985. Anticholinesterase agents. In Goodman and Gilman's The pharmacological basis of therapeutics. New York, NY: MacMillan Publishing Co., Ch. 6, 110-129.
- Thornton, R., Caldwell, J. L., Clark, W., Guardiani, F., and Rosario, J. 1992a. Effects on physiology and performance of wearing the aviator NBC ensemble while flying the UH-60 helicopter flight simulator in a controlled heat environment. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory. USAARL report (in press).

Thornton, R., Caldwell, J. L., Guardiani, F., and Pearson, J. 1992b. Effects of microclimate cooling on physiology and performance while flying the UH-60 helicopter simulator in NBC conditions in a controlled heat environment. Fort Rucker, AL: U.S. Army Aeromedical Research Laboratory. USAARL report (in press).

Ursano, R. J. 1988. Combat stress in the chemical and biological warfare environment. Aviation, space, and environmental medicine, 59(12):1123-1124.

Vojvodic, V., and Boskovic, B. 1974. A comparative study of pralidoxime, obidoxime, and trimedoxime in healthy men volunteers and in rats. In Medical protection against chemical-warfare agents, Stockholm International Peace Research Institute, Stockholm, Sweden: Almquist and Wiksell International. Cited in Headley, 1985 (above).

Weiner, N. 1985. Atropine, scopolamine, and related antimuscarinic drugs. In Goodman and Gilman's The pharmacological basis of therapeutics. New York, NY: MacMillan Publishing Co., Ch. 7, 130-144.