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USE OF AUTO-INJECTORS BY CIVILIAN EMERGENCY MEDICAL PERSONNEL TO TREAT CIVILIANS EXPOSED TO NERVE AGENT©

STUDY GUIDE

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Preface

This **Study Guide** has been developed for use in a Federal Emergency Management Agency training course on **Use of Auto-Injectors by Civilian Emergency Medical Personnel to Treat Civilians Exposed to Nerve Agent** for the CSEPP (Chemical Stockpile Emergency Preparedness Program). The course is largely based on the detailed literature provided by the manufacturer of the auto-injectors, developed in concert with the federal Food and Drug Administration. You will also find specific references to related materials already developed for the CSEPP that may be useful in learning about the use of auto-injectors. It is likely that this course may be taught at the same time as or as a module in the Agent Characteristics and Toxicity First Aid and Special Treatment (ACT FAST) Course.

Much of this material is derived directly from user pamphlets from Survival Technology, Inc. Additional materials and review were provided by Fred Sidell, MD, U.S. Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, MD; Charles Geis, U. S. Army Defense Ammunition Center & School, Savanna, IL; Phyllis G. Thompson and Robert Norville, FEMA; and Annetta P. Watson and Kathy S. Gant, ORNL. One or more of the illustrations were produced by Cinetel Productions, Knoxville, TN, as a part of the animation for the **Chemical Stockpile Agent Characteristics and Effects** videotape.[1] Lori Warneke has managed the production of this Study Guide and all related training materials for this course.

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LEARNING OBJECTIVES

The objectives of the training module are to allow the participants to:

- Identify the antidotes to be administered in the event of nerve agent exposure,
- Identify the conditions under which antidote auto-injectors should be used,
- Demonstrate the use of the antidote auto-injectors, and
- Recognize adverse reactions to the use of the antidotes.

WHAT AUTO-INJECTORS ARE

Auto-injectors are simple, compact injection systems that come equipped with a pre-measured amount (adult dose) of antidote. An antidote relieves or counters the effects of poisons such as nerve agents. NOTE: Use of antidotes will **not** protect from **anticipated exposures**; they should be used only when signs and symptoms of exposure are present.

Auto-injectors
- permit rapid injection of the required antidotes;
- prevent the needle from being subjected to cross-contamination; and
- enable rapid and accurate administration even if the care giver and patient are in protective clothing.

Auto-injectors facilitate timely treatment by providing
- simple, accurate, rapid drug administration;
- a pre-measured, controlled dose;
- no vials, ampules or syringes to manipulate;
- fully automatic operation; and
- rugged construction.

Food and Drug Administration (FDA)-approved and commercially available auto-injectors containing pre-measured doses of the nerve agent antidotes atropine and 2-PAM chloride (2-PAM Cl, pralidoxime chloride or PROTOPAM® CHLORIDE) are available for use by civilian emergency medical personnel in the event of an accidental release of nerve agent within the Chemical Stockpile Emergency Preparedness Program (CSEPP) states, if the states choose and are able legally to use them.

One U.S.-based manufacturer (Survival Technology, Inc. [STI][2]) has FDA approval to manufacture auto-injectors containing atropine and 2-PAM Cl. Known as AtroPen® and Pralidoxime Chloride Auto-Injectors, these auto-injectors contain pre-measured amounts of atropine (2 mg) and 2-PAM Cl (600 mg), antidotes used in instances of exposure to nerve agent. These are available to local and state health authorities. These auto-injectors have been approved by FDA for civilian use in incidents involving nerve agents and organophosphorus (OP) insecticides.[2] There are also several other types of auto-injectors available for civilian use to fulfill other medical pharmaceutical needs, such as treating allergic reactions.

Background

STI introduced the concept of auto-injector self-administration to the military medical community in response to a need to administer emergency drugs safely and very rapidly to patients who are at risk of death if they do not receive the drug. STI has supplied over 65 million auto-injectors to the U.S. Department of Defense and allies since 1958.[3]

STI auto-injectors are used in the civilian sector as well. During the war with Iraq in the early 1990s, STI supplied Israel with nerve agent antidote auto-injectors for patient self-administration by the civilian population (children and adults). Data from the Israel wartime experience regarding the relatively mild effects of accidentally administered doses of atropine via auto-injectors to children who had not been exposed to nerve agents indicate that, while atropine doses were up to 17- fold higher than the standard doses for age, no seizures or life-threatening complications were reported.[4]

WHAT AUTO-INJECTORS CONTAIN

The AtroPen® Auto-Injector is a self-contained unit for the automatic administration of atropine. Each AtroPen® contains: 1.67 mg atropine (equivalent to 2 mg atropine sulfate); 12.47 mg glycerin; and 2.8 mg phenol in a citrate buffer and sterile water for injection.[5]

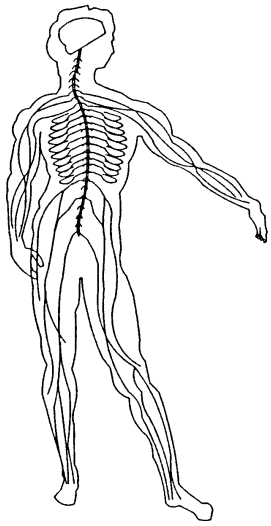
2-PAM Cl is commercially available as a soluble white powder; as a water-based solution it is available only in auto-injectors. Individual syringe delivery introduces time constraints—2 minutes to dissolve the commercial powder in sterile water in addition to time needed for preparation and filling of the syringe (personal communication, F. R. Sidell)[6]— and greater opportunities for human error (weighing, mixing, etc.) during a time-critical medical emergency event. Injection via auto-injector provides 2-PAM Cl in a sterile solution for immediate intramuscular injection. Each prefilled auto-injector provides 600 mg of the antidote in a self-contained unit, specially designed for administration by adequately trained civilian emergency medical personnel. The auto-injector contains 600 mg 2-PAM Cl in 2 ml sterile solution containing 20 mg/ml benzyl alcohol, 11.26 mg/ml aminoacetic acid and water, pH adjustment 2.0–3.0 by hydrochloric acid.[3]

Recommended treatment for low-dose effects of nerve agent exposure [pinpoint pupils (miosis), runny nose and shortness of breath] in healthy male and female adults is administration of 1 dose of atropine (2 mg) and 1 dose of 2-PAM Cl (600 mg). For more serious cases, 3 to 5 doses of atropine and up to 3 doses of 2-PAM Cl may be needed.

HOW THE ANTIDOTES WORK

The nervous system controls body functions through the use of chemicals which act as "instructions" to nerves and to the muscles and glands. These instructions come in two forms: stimulate (move or work) and relax (stop or rest). When a nerve agent is present, it interferes with the normal chemical instructions that direct the muscle (or gland) to return to an unstimulated state and relax or rest.[1,7,8]

By interfering with the normal chemical checks and balances, the action of toxic nerve agents overstimulates the nerve endings and central nervous system. Overstimulation of the nervous system causes muscles and certain glands to over-react and the various body organs to malfunction.[1,7,8]



The initial treatment for nerve agent exposure comes as a two-part antidote: (1) atropine to stop the effect of the nerve agent, and (2) 2-PAM chloride to restore the normal muscle function by removing the agent.[1,7,8]

Atropine stops the effect of the nerve agent by blocking the effects of over-stimulation. It effectively antagonizes the actions of the organophosphate nerve agent at certain nerve receptors. This antidote relieves the smooth muscle constriction in the lungs and gastrointestinal tract and dries up respiratory tract secretions.[1,5,7,8]

The companion drug to atropine is 2-PAM Cl. 2-PAM Cl complements or completes the action of atropine. It is an oxime drug that acts to restore normal functions at the nerve synapse by removing organophosphate nerve agent from cholinesterase (mainly outside of the central nervous system) and reactivating the cholinesterase. This antidote is effective at re-establishing normal skeletal muscle contraction (relieves twitching and paralysis of respiratory muscles).[1,3,7,8] Because 2-PAM Cl is less effective in relieving depression of the respiratory center, atropine is always first required to block the effect of accumulated acetylcholine at this site. 2-PAM Cl relieves smooth muscle (muscarinic) signs and symptoms, salivation, bronchospasm (constriction of the air passages of the lung by contraction of the bronchial muscles), etc., but this action is relatively unimportant since atropine is adequate for this purpose.[3,5]

2-PAM Cl is distributed throughout the extra-cellular water; it is not bound to plasma protein. The drug is rapidly excreted in the urine. Consequently, 2-PAM Cl is relatively short-acting. Repeated doses may be needed, especially where there is any evidence of continuing absorption of the nerve agent.[3]

The minimum therapeutic concentration of 2-PAM Cl in blood plasma is 4 μg/ml. This level is reached in about 16 minutes after a single injection of 600 mg 2-PAM Cl. The apparent half-life of 2-PAM Cl in the human body is 74–77 minutes.[3]

WHO CAN USE AUTO-INJECTORS

There has been concern that use of auto-injectors could lead to administration of inappropriate and harmful doses to civilians during emergency situations. While pre-measured doses in auto-injectors should be safe for civilians who meet the profile of military personnel (e.g., approximate ages of 18–35, weight at least 70 kg or 154 pounds, healthy with no compromising medical conditions), it has been standard medical policy that age, sex, weight and health of all other patients must first be considered when determining the amount of atropine and 2-PAM Cl to administer. The amount to be administered may need to be adjusted if the patient does not meet the military personnel profile. Detailed tables to assist with this determination have been included in the ACT FAST Study Guide.[7]

"**Pralidoxime (2-PAM Cl) in the auto-injector may also be administered by qualified civilian emergency responders who have had adequate training in the on-site recognition and treatment of nerve agent intoxication in the event of an accidental release of nerve agent."** This language was included on the pharmaceutical data sheet from STI after consultation with the Centers for Disease Control and review and approval by the FDA.[3]

The majority of the CSEPP States tend to follow the U.S. Department of Transportation's national curriculum for Emergency Medical Technicians. This curriculum generally restricts training on use of IVs to Intermediate Emergency Medical Technicians and paramedics. However, some states are considering the use of auto-injectors in treating nerve agent exposure.[7] Review of each state's laws and regulations will be needed to determine appropriate use of the auto-injectors within each state.

HOW AND WHEN TO USE AUTO-INJECTORS

The 2-PAM Cl and atropine auto-injectors should be used by qualified civilian emergency medical personnel only after the following events have occurred:[3,5]

- emergency medical personnel have donned personal protective equipment subsequent to recognizing the existence of a chemical agent hazard in area
- some or all of the symptoms of nerve agent poisoning cited below are present:
  - —unexplained runny nose
  - —tightness of chest with difficulty in breathing
  - —pinpointed pupils of the eye, resulting in blurred vision (miosis)
  - —drooling, excessive sweating
  - —nausea, vomiting, and abdominal cramps
  - —involuntary urination and defecation
  - —jerking, twitching, and staggering
  - —headache, drowsiness, coma, convulsions
  - —stoppage of breathing

Cinetel Productions

Signs and Symptoms of Nerve Agent Exposure[3]

MILD	• headache, blurred vision and pinpoint pupils (miosis), tight chest (smooth muscle constrictions), excessive sweating, tearing (lacrimation), salivation, unexplained runny nose
MODERATELY SEVERE	• severe tightness in the chest, diarrhea (rare)
VERY SEVERE	• bluish discoloration of skin (cyanosis), respiratory failure, coma, unconscious, convulsions

Appropriate steps must be taken to insure that personnel equipped with auto-injectors understand their use, including familiarity with symptoms of poisoning and operation of the auto-injector.

Treatment For Exposure To Nerve Agents

- Depending on the severity of symptoms, immediately administer one (1) atropine auto-injector, followed by one (1) 2-PAM Cl auto-injector.
- Atropine must be given first until its effects become apparent; only then should 2-PAM Cl be administered. Sometimes more than one injector of atropine is used before giving any 2-PAM Cl.
- If nerve agent signs or symptoms are still present after 5–10 minutes, repeat injections.
- If signs or symptoms still exist after an additional 10 minutes, repeat injections for a third time.
- If signs or symptoms remain after the third set of injections, do not give any more antidotes but seek medical help immediately.[3] By this time, you may have used three to five (3–5) injectors of atropine and up to three (3) of 2-PAM Cl for more serious cases.

If severe signs and symptoms are present:

- In cases of very severe exposure, all three auto-injector kits (atropine and 2-PAM Cl) should be administered in rapid succession; then medical help should be sought.
- Remove secretions, maintain patient's airway and, if necessary, use artificial ventilation.
- Morphine, theophylline, aminophylline, or succincylcholine should not be used with 2-PAM Cl. Tranquilizers of the reserpine or phenothiazine type are to be avoided.
- "Pralidoxime (2-PAM Cl) is most effective if administered immediately after poisoning. Generally, little is accomplished if the drug is given more than 6 hours after termination of exposure. When the nerve agent has been ingested, however, exposure may continue for some time due to slow absorption from the lower bowel, and fatal relapses have been reported after initial improvement. Continued administration for several days may be useful in such patients. Close supervision of the patient is necessary for at least 48 to 72 hours. If dermal exposure has occurred, clothing should be removed and the hair and skin washed thoroughly with sodium bicarbonate or alcohol as soon as possible. (Note: The CSEPP recommends the use of bleach and water.) Diazepam (Valium®) may be given cautiously if convulsions are not controlled by atropine."[11]

Precautions

Any patient sick enough to receive even one dose of atropine should immediately be placed under medical observation for at least 24 hours, since signs or symptoms of nerve agent poisoning may reappear. Such observation permits determination as to whether additional medical measures should be taken.[5] **If atropine is used to treat infants, smaller amounts should be given.**[6]

It is not known whether 2-PAM Cl is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when 2-PAM Cl is administered to a nursing woman; if 2-PAM Cl is used, use of substitutes for mother's milk is advised. Safety and effectiveness of 2-PAM Cl in children have not been established.[3]

Adverse Reactions

Forty (40) to sixty (60) minutes after intramuscular injection of 2-PAM Cl, mild to moderate pain may be experienced at the site of injection. In a normal person, 2-PAM Cl may cause

- blurred vision,
- double vision (diplopia) and impaired accommodation,
- dizziness,
- headache,
- drowsiness,
- nausea,
- rapid heart rate (tachycardia),
- increased systolic and diastolic blood pressure, and
- hyperventilation.

Overdosage

If excessive atropine is administered, the signs of atropinization listed above will become even more severe and the patient may also develop

- blurring of vision,
- delirium, and
- urinary retention.

When signs and symptoms of atropinization develop, further administration of atropine should be withheld until the evidence of atropinization subsides.[5]

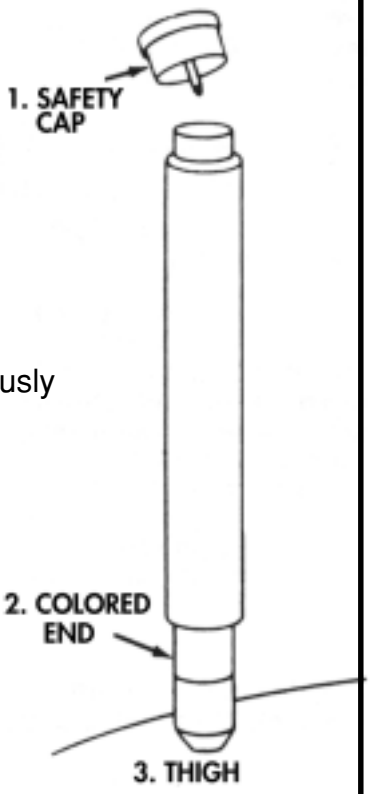
In the case of 2-PAM Cl, the following has been observed in non-exposed subjects only: dizziness, blurred vision, double vision (diplopia), headache, impaired accommodation, nausea, slightly rapid heart rate (tachycardia). In therapy it has been difficult to differentiate side effects due to the antidote drug from those due to the effects of the nerve agent or organophosphorus insecticide.[3]

Artificial respiration and other supportive therapy should be administered as needed.

Directions for Use

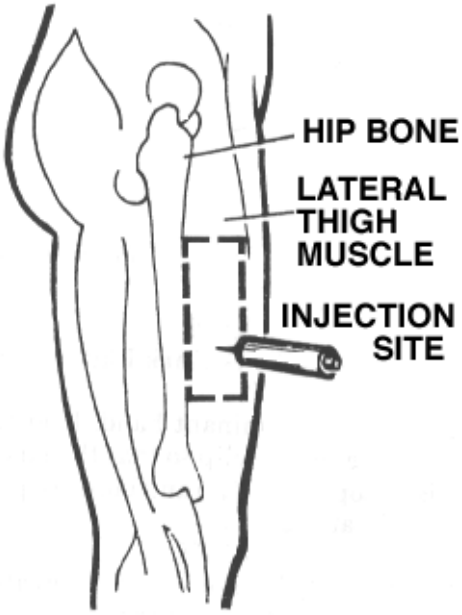
When auto-injector use is indicated, the recommended procedure is to inject the contents of the auto-injector into the muscles of an auterolateral thigh (through pocket).[3,5] Proceed as follows:

1. Remove safety cap (**yellow** on atropine; **gray** on 2-PAM Cl; both in clip on Mark I.). Do not touch the colored end of the injector after removing the safety cap, since the injector can and will function into the fingers or hand if any pressure is applied to this end of the injector.



2. Hold injector as you would a pen. Place colored end (**green** on atropine, **black** on 2-PAM Cl) on thickest part of thigh and press hard until injector functions. Pressure automatically activates the spring, which plunges the needle into the muscle and simultaneously forces fluid through it into the muscle tissues.

3. Hold firmly in place for ten seconds, then remove. Massage the area of injection.



4. After each auto-injector has been activated, the empty container should be disposed of properly. It cannot be refilled nor can the protruding needle be retracted. It should be disposed of in a "sharps" container in accordance with rules for handling medical wastes and possible blood-borne pathogens. Dosage should be noted on a triage tag or written on the chest or forehead of the patient

IMPORTANT: Physicians and/or other medical personnel assisting evacuated victims of nerve agent exposure, should avoid exposing themselves to cross-contamination by ensuring that they do not come into contact with the patients' clothing.

OBTAINING AND CARING FOR AUTO-INJECTOR SUPPLIES

Auto-injectors are supplied through the Directorate of Medical Material, Defense Personnel Support Center or other analogous local, state, or federal agencies. The atropine and 2-PAM Cl auto-injectors have a five-year shelf life, making them suitable for storage in emergency stockpiles. Store the auto-injectors at room temperature (approximately 25°C, 77°F). Keep them from freezing.[3]

Auto-injectors freeze at temperatures below 29F. Injection using the auto-injector is more difficult when emergency workers are wearing cold-weather clothing in addition to the PPE. Auto-injectors should not be carried in the external pocket of the BDO when the temperature is below freezing. Place them in an inner pocket where body heat will keep them warm. A string should be tied to the auto-injector, and threaded through the outer layers of clothing and tied to an outside pocket or belt. The auto-injector can be rapidly extracted from within the clothing by pulling the string.[17]

Frozen auto-injectors are still usable after being thawed if they do not appear broken or cracked.[17]

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