

# Acetylcholinesterase Inhibitors (Carbamates, Nerve Agents, Organophosphates) Exposure

## Aliases

Acetylcholinesterase inhibitor, ATNAA®, carbamate, Duodote®, insecticide, nerve agent, organophosphate, pesticide, weapons of mass destruction, WMD

## Patient Care Goals

Rapid recognition of the signs and symptoms of confirmed or suspected acetylcholinesterase inhibitor (AChEI) agents such as carbamates, nerve agents, or organophosphates exposure followed by expeditious and repeated administration of atropine, the primary antidote

**Note:** Carbamates and organophosphates are commonly active agents in over-the-counter insecticides. Accidental carbamate exposure rarely requires treatment

## Patient Presentation

### Inclusion Criteria

1. **DUMBELS** is a mnemonic used to describe the signs and symptoms of acetylcholinesterase inhibitor agent poisoning. All patient age groups are included where the signs and symptoms exhibited are consistent with the toxidrome of DUMBELS.
  - a. Diarrhea
  - b. Urination
  - c. Miosis or Muscle weakness
  - d. Bronchospasm, Bronchorrhea, Bradycardia (the killer B's)
  - e. Emesis
  - f. Lacrimation
  - g. Salivation or Sweating

### Exclusion Criteria

No recommendations

## Patient Management

1. Don the appropriate PPE; ensure rescuers are properly trained and equipped.
2. Remove the patient's clothing and wash the skin with soap and water. Be aware that:
  - a. Acetylcholinesterase inhibitor agents can be absorbed through the skin.
  - b. Contaminated clothing can provide a source of continued exposure to the toxin.
3. Rapidly assess the patient's respiratory status, mental status, and pupillary status.
4. Administer the antidote-autoinjector (if available) **[ALL EMS PRACTICE LEVELS]** immediately for confirmed or suspected acetylcholinesterase inhibitor agent exposure.
5. Administer oxygen as appropriate for dyspnea or distress with a target of achieving greater than 93% saturation for most acutely ill patients.
6. Provide airway management.
7. Establish intravenous access **[AEMT]** (if possible).
8. Apply an ECG cardiac monitor (if available).
9. Recognize that the heart rate may be normal, bradycardic, or tachycardic.
10. Characterize clinical improvement based upon the drying of secretions and easing of respiratory effort rather than heart rate or pupillary response.
11. Reassess patient status continuously; this is critical.

## Assessment Considerations

1. Acetylcholinesterase inhibitor agents are highly toxic chemical agents and can rapidly be fatal.
2. Patients with low-dose chronic exposures may have a more delayed presentation of symptoms.

3. Antidotes (atropine and pralidoxime) are effective if administered before circulation fails.
4. The patient may develop:
  - a. Miosis (pinpoint pupils).
  - b. Bronchospasm.
  - c. Bradycardia.
  - d. Vomiting.
  - e. Excessive secretions in the form of:
    - i. Tearing.
    - ii. Salivation.
    - iii. Rhinorrhea.
    - iv. Diarrhea.
    - v. Urination.
    - vi. Bronchorrhea.
5. Penetration of an acetylcholinesterase inhibitor agent into the central nervous system (CNS) will cause:
  - a. Headache.
  - b. Confusion.
  - c. Generalized muscle weakness.
  - d. Seizures.
  - e. Lethargy or unresponsiveness.
6. **Estimated level of exposure based upon signs and symptoms**
  - a. **Mild**
    - i. **Miosis alone (while this is a primary sign in vapor exposure, it may not be present in all exposures)**
    - ii. **Miosis and severe rhinorrhea**
  - b. **Mild to moderate (in addition to symptoms of mild exposure)**
    - i. **Localized swelling**
    - ii. **Muscle fasciculation**
    - iii. **Nausea and vomiting**
    - iv. **Weakness**
    - v. **Shortness of breath**
  - c. **Severe (in addition to symptoms of mild to moderate exposure)**
    - i. **Unconsciousness**
    - ii. **Convulsions**
    - iii. **Apnea or severe respiratory distress requiring assisted ventilation**
    - iv. **Flaccid paralysis**
7. Onset of symptoms can be immediate with an exposure to a large amount of the acetylcholinesterase inhibitor.
  - a. There is usually an asymptomatic interval of minutes after liquid exposure before these symptoms occur.
  - b. Effects from vapor exposure occur almost immediately.
8. Signs and symptoms with large acetylcholinesterase inhibitor agent exposures (regardless of route)
  - a. Sudden loss of consciousness
  - b. Seizures
  - c. Copious secretions
  - d. Apnea
  - e. Death
9. Obtain an accurate exposure/ingestion history (as patient may become unconscious before arrival at ED):
  - a. Time of ingestion or exposure
  - b. Route of exposure
  - c. Quantity of medication or toxin taken (safely collect all possible medications or agents)
  - d. Alcohol or other intoxicant taken
  - e. Pertinent cardiovascular history or other prescribed medications for underlying disease
10. The patient can manifest any or all of the signs and symptoms of the toxidrome based on the route of exposure, agent involved, and concentration of the agent:

- a. Vapor exposures will have a direct effect on the eyes and pupils causing miosis.
  - b. Patients with isolated skin exposures will have normally reactive pupils.
  - c. Certain acetylcholinesterase inhibitor agents can place the patient at risk for both a vapor and skin exposure.
11. If there is a severe exposure to one patient, suspected multiple victims, or concerns for a widespread chemical release (unintentional or intentional)
- a. Provide early notification of intended destination hospital
  - b. Consider activation/obtaining the Chem Pack for additional atropine, pralidoxime and benzodiazepine doses
    - i. MedEvac Communication Center (800-888-8056) has list of Chem Pack location and contact information

### Treatment and Interventions (see dosing tables below)

#### 1. Medications:

##### a. Atropine

- Atropine is the primary antidote for organophosphate, carbamate, or nerve agent exposures, and repeated doses should be administered liberally to patients who exhibit signs and symptoms of exposure or toxicity.
- Atropine should be administered immediately followed by repeated doses until the patient's secretions resolve
- [Auto-Injector: **ALL EMS PRACTICE LEVELS; IV/IM: PARA**]
  1. **IV Adult: 1-2 mg every 5 minutes until symptomatic improvement**
  2. **IV Pediatric: 0.02 mg every 5 minutes until symptomatic improvement**
  3. **IM Dosing: See Tables Below with Dosing Recommendations**
  4. Atropine needed to treatment the patient may be extremely large exceeding typical EMS or hospital stocking amounts.
    - i. Consider early activation of Chem Pack
    - ii. Consider arranging for additional doses for atropine along route for longer distance inter-facility transports

##### b. Pralidoxime chloride (2-PAM) (ChemPack/From hospital/Interfacility)

- Pralidoxime chloride is a secondary treatment and should be given concurrently in an effort to reactivate the acetylcholinesterase.
- Dosing [Auto-Injector: **ALL EMS PRACTICE LEVELS; IV/IM: PARA**]
  1. **IV Adult: 1-2g over 15-30 minutes, may be repeat after 1 hour for ongoing symptoms; 10mg/kg/hr infusion X 24 hours after bolus**
  2. **IV Pediatric: 20-50mg/kg (2mg maximum) over 15-30 minutes, may be repeat after 1 hour for ongoing symptoms; 10-20mg/kg/hr infusion X 24 hours after bolus**
  3. **IM Dosing: See Tables Below with Dosing Recommendations**
- In order to be beneficial to the victim, a dose of pralidoxime chloride should be administered shortly after the nerve agent or organophosphate poisoning as it has minimal clinical effect if administration is delayed.

##### c. Benzodiazepines [PARA]

- Benzodiazepines are administered as an anticonvulsant for those patients who exhibit seizure activity [see Seizures guideline for doses and routes of administration].
- Midazolam or diazepam is preferable due to their more rapid onset of action.
- See Tables Below with Dosing Recommendations

### Mild Acetylcholinesterase Inhibitor Agent Exposure

<b>Patient (Weight)</b>	<b>Atropine Dose IM or via Auto-Injector</b>
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<b>Infant:</b>	0.05 mg/kg IM or via auto-
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0–2 yo	injector ( <i>e.g. 0.25 and/or 0.5 mg auto-injector(s)</i> )
<b>Child:</b> 3–7 yo (13–25 kg)	1 mg IM or via auto-injector ( <i>e.g. one 1 mg or two 0.5 mg auto-injectors</i> )
<b>Child:</b> 8–14 yo (26–50 kg)	2 mg IM or via auto-injector ( <i>e.g. one 2 mg or two 1 mg auto-injectors</i> )
<b>Adolescent/ Adult</b>	2 mg IM or via auto-injector
<b>Pregnant Women</b>	2 mg IM or via auto-injector
<b>Geriatric/ Frail</b>	1 mg IM or via auto-injector

#### Mild to Moderate Acetylcholinesterase Inhibitor Agent Exposure

Patient (Weight)	Atropine Dose IM or via Auto- Injector	Pralidoxime Chloride Dose IM or via 600 mg Auto- Injector
<b>Infant:</b> 0–2 years	0.05 mg/kg IM or via auto-injector ( <i>e.g. 0.25 mg and/or 0.5 mg auto- injector</i> )	15 mg/kg IM
<b>Child:</b> 3–7 yo (13–25 kg)	1 mg IM or via auto- injector ( <i>e.g. one 1 mg auto- injector or two 0.5 mg auto- injectors</i> )	15 mg/kg IM <b>OR</b> One auto- injector (600 mg)
<b>Child:</b> 8–14 yo (26–50 kg)	2 mg IM or via auto- injector ( <i>e.g. one 2 mg auto-injector or two 1 mg auto-</i>	15 mg/kg IM <b>OR</b> One auto- injector (600 mg)

*injectors)*

<b>Adolescent/ Adult</b>	2–4 mg IM or	600 mg IM
	via auto- injector	<b>OR</b> One auto- injector (600 mg)

<b>Pregnant Women</b>	2–4 mg IM or	600 mg IM
	via auto- injector	<b>OR</b> One auto- injector (600 mg)

<b>Geriatric/ Frail</b>	2 mg IM or	10 mg/kg IM
	via auto- injector	<b>OR</b> One auto- injector (600 mg)

### Severe Acetylcholinesterase Inhibitor Agent Exposure

<b>Patient (Weight)</b>	<b>Atropine Dose IM or via Auto- Injector</b>	<b>Pralidoxime Chloride Dose IM or via 600 mg Auto- Injector</b>
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<b>Infant:</b> 0–2 yo	0.1 mg/kg IM or via auto- injector ( <i>e.g.</i> 0.25 <i>mg and/or</i> 0.5 <i>mg</i> <i>auto- injector</i> )	45 mg/kg IM
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<b>Child:</b> 3–7 yo (13–25 kg)	0.1 mg/kg IM	45 mg/kg IM
	<b>OR</b> 2 mg via auto- injector ( <i>e.g.</i> <i>one</i> 2 <i>mg auto- injector or</i> <i>four</i> 0.5 <i>mg</i> <i>auto- injectors</i> )	

<b>Child:</b> 8–14 yo	4 mg IM or via auto- injector	45 mg/kg IM <b>OR</b> Two auto-
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(26–50 kg)	( <i>e.g. two 2 mg auto-injectors or four 1 mg auto-injectors</i> )	injectors (1200 mg)
<b>Adolescent:</b> 14 yo or older	6 mg IM or via auto-injector ( <i>e.g. three 2 mg auto-injectors</i> )	Three auto-injectors (1800 mg)
<b>Adult</b>	6 mg IM or via auto-injector ( <i>e.g. three 2 mg auto-injectors</i> )	Three auto-injectors (1800 mg)
<b>Pregnant Women</b>	6 mg IM or via auto-injector ( <i>e.g. three 2 mg auto-injectors</i> )	Three auto-injectors (1800 mg)
<b>Geriatric/Frail</b>	2-4 mg IM or via auto-injector ( <i>e.g. one to two 2 mg auto-injectors</i> )	25 mg/kg IM <b>OR</b> two to three auto-injectors (1200 mg–1800 mg)

### Guidance for the Treatment of Seizures Secondary to Acetylcholinesterase Inhibitor Agent Exposure

Patient	Diazepam	Midazolam
	0.2–0.5 mg/kg IM Repeat every 2-5 minutes	0.2 mg/kg IM Repeat prn in 10 minutes
<b>Infant</b> (0–2 yo)	0.2–0.5 mg/kg IV every 15-30 minutes May repeat twice as needed	May repeat dose once
	Total	Total

	maximum dose: 5 mg	maximum dose: 0.4 mg/kg
	0.2–0.5 mg/kg IM Repeat every 2–5 minutes	0.2 mg/kg IM Not to exceed 10 mg Repeat prn in 10 minutes
	0.2–0.5 mg/kg IV every 15-30 minutes May repeat dose twice if needed	May repeat dose once
<b>Child</b> (3–13 yo)	Total maximum dose: 5 mg if less than 5 years	Total maximum dose: 0.4 mg/kg Not to exceed 20 mg
	Total maximum dose: 10 mg if age 5 years or older 1 CANA® auto-injector	Not to exceed 20 mg
		0.2 mg/kg IM Total maximum dose of 10 mg Repeat prn in 10 minutes
<b>Adolescent</b> (14 yo or older)	2–3 CANA® auto-injectors	
	5–10 mg IV every 15 minutes	May repeat dose once
	Total maximum dose: 30 mg	Total maximum dose: 20 mg
	2–3 CANA® auto-injectors	10 mg IM Repeat prn in 10 minutes
<b>Adult</b>	5–10 mg IV every 15	May repeat dose once

minutes

Total maximum dose: 30 mg	Total maximum dose: 20 mg
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2–3 CANA® auto-injectors	10 mg IM Repeat prn in 10 minutes
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**Pregnant  
Women**

5–10 mg IV every 15 minutes	May repeat dose once
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Total maximum dose: 30 mg	Total maximum dose: 20 mg
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2–3 CANA® auto-injectors	10 mg IM Repeat prn in 10 minutes
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**Geriatric**

5–10 mg IV every 15 minutes	May repeat dose once
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Total maximum dose: 30 mg	Total maximum dose: 20 mg
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**Tables adapted from:** U.S. Department of Health and Human Services, ASPR, National Library of Medicine, *Chemical Hazards Emergency Medical Management: Nerve Agents-Prehospital Management*, [www.chemm.nlm.nih.gov](http://www.chemm.nlm.nih.gov)

**Auto-injectors Information for Treatment of Acetylcholinesterase Inhibitor Exposure**

1. Mark I® Kits [**ALL EMS PRACTICE LEVELS-O**]
  - a. A commercially available kit of nerve agent/organophosphate antidote auto- injectors. These are being phased out and replaced with Duodote by the CDC
  - b. A Mark I® kit consists of one auto-injector containing 2 milligrams of atropine and a second auto-injector containing 600 milligrams of pralidoxime chloride
2. Duodote® [**ALL EMS PRACTICE LEVELS-O**]
  - a. A commercially available auto-injector of nerve agent/organophosphate antidote
  - b. Duodote® is one auto-injector that contains 2.1 milligrams of atropine and 600 milligrams of pralidoxime chloride
3. ATNAA® (Antidote Treatment Nerve Agent Auto-injector) [**ALL EMS PRACTICE LEVELS-O**]
  - a. An auto-injector of nerve agent/organophosphate antidote that is typically in military supplies
  - b. ATNAA® is one auto-injector that contains 2.1 milligrams of atropine and 600 milligrams of pralidoxime chloride
  - c. ATNAA® may be seen in civilian supplies assets when Duodote® is unavailable or in short supply
4. CANA® (Convulsive Antidote Nerve Agent) is a commercially available auto- injector that contains 10 mg of diazepam [**ALL EMS PRACTICE LEVELS-O**]

## **CHEMPACK [ALL EMS PRACTICE LEVELS-OJ]**

1. Federally-owned cache of nerve agent antidotes that is managed by the Centers for Disease Control and Prevention (CDC) and offered to states that voluntarily agree to maintain custody and security of CHEMPACK assets
2. These are forward-deployed at sites determined by states that are part of the program such as hospitals and EMS centers
3. Deployment of CHEMPACKs are reserved for events where the nerve agent/organophosphate exposure will deplete the local or regional supply of antidotes
4. There are two types of CHEMPACK containers:
  - a. **EMS Containers:** CHEMPACK assets for EMS contain a large portion of auto-injectors for rapid administration of antidotes by EMS providers of all levels of licensure/certification – They contain enough antidote to treat roughly 454 patients
  - b. **Hospital Containers:** CHEMPACK assets contain a large portion of multidose vials and powders for reconstitution – they contain enough antidote to treat roughly 1000 patients
5. MedEvac Communication Center (800-888-8056) has list of Chem Pack location and contact information

### **Medications/Auto-Injector Administration Considerations**

- The medication dosing tables that are provided above are based upon the severity of the clinical signs and symptoms exhibited by the patient. There are several imperative factors to note:
  - For organophosphate or severe acetylcholinesterase inhibitor agent exposure, the required dose of atropine necessary to dry secretions and improve the respiratory status is likely to exceed 20 mg. Atropine should be administered rapidly and repeatedly until the patient's clinical symptoms diminish. Atropine must be given until the acetylcholinesterase inhibitor agent has been metabolized. It may require up to 2000 mg of atropine over several days to weeks
  - Since the antidotes in the Mark I® kit are in two separate vials, the atropine auto-injector in the kit can be administered to the patient in the event that Atro-Pen® or generic atropine auto-injectors are not available and/or intravenous atropine is not an immediate option
  - Due to the fact that Duodote® auto-injectors contain pralidoxime chloride, they should not be used for additional dosing of atropine beyond the recommended administered dose of pralidoxime chloride
  - All of the medications can be administered intravenously in the same doses cited for the intramuscular route. However, due to the rapidity of onset of signs, symptoms, and potential death from acetylcholinesterase inhibitor agents, intramuscular administration is highly recommended to eliminate the inherent delay associated with establishing intravenous access
  - The antidotes can be administered via the intraosseous route. However, due to the rapidity of onset of signs, symptoms, and potential death from acetylcholinesterase inhibitor agents, intramuscular administration remains the preferable due to the inherent delay associated with establishing intraosseous access and the limited use of this route of administration for other medications

### **Patient Safety Considerations**

- Continuous and ongoing patient reassessment is critical.
- Clinical response to treatment is demonstrated by the drying of secretion and the easing of respiratory effort.
- Initiation of and ongoing treatment should not be based upon heart rate or pupillary response.
- Precautions for pralidoxime chloride administration:
  - Although Duodote® and ATNAA® contain atropine (the primary antidote for an acetylcholinesterase inhibitor agent poisoning), the inclusion of pralidoxime chloride in the auto-injector can present challenges if additional doses of atropine are warranted by the patient condition and other formulations of atropine are unavailable:
    - Pediatrics: An overdose of pralidoxime chloride may cause profound

neuromuscular weakness and subsequent respiratory depression.

- Adults: Especially for the geriatric victim, excessive doses of pralidoxime chloride may cause severe systolic and diastolic hypertension, neuromuscular weakness, headache, tachycardia, and visual impairment.
- Geriatrics: In a victim who may have underlying medical conditions, particularly impaired kidney function or hypertension, the EMS provider should consider administering the lower recommended adult dose of intravenous pralidoxime chloride.

### **Considerations during the use of auto-injectors**

- If an auto-injector is administered, a dose calculation prior to administration is not necessary.
- For atropine, additional auto-injectors should be administered until secretions diminish.
- Mark I® kits, Duodote® and ATNAA® have not been approved for pediatric use by the Food and Drug Administration (FDA), but they can be considered for the initial treatment of children of any age with severe symptoms of an Acetylcholinesterase inhibitor agent poisoning, especially if other formulations of atropine are unavailable.
- Pediatric Atro-Pen® auto-injectors are commercially available in a 0.25 mg auto-injector (yellow) and a 0.5 mg auto-injector (red). Atro-Pen® auto-injectors are commercially available in a 1 mg auto-injector (blue) and a 2 mg auto-injector (green).
- A pralidoxime chloride 600 mg auto-injector may be administered to an infant that weighs greater than 12 kg.

### **Notes and Educational Pearls Key Considerations**

- Clinical effects of acetylcholinesterase inhibitor agents
- The clinical effects are caused by the inhibition of the enzyme acetylcholinesterase which allows excess acetylcholine to accumulate in the nervous system.
- The excess accumulated acetylcholine causes hyperactivity in muscles, glands, and nerves.
- Organophosphates (certain insecticides)
- Organophosphates can be legally purchased by the general public.
- Organophosphates (e.g. pesticides) penetrate tissues and bind to the patient's body fat producing a prolonged period of illness and ongoing toxicity even during aggressive treatment.
- Nerve agents
  - Traditionally classified as weapons of mass destruction (WMD)
  - Not readily accessible to the general public
  - Extremely toxic and rapidly fatal with any route of exposure
  - GA (tabun), GB (sarin), GD (soman), GF, and VX are types of nerve agents and are WMDs
  - Nerve agents can persist in the environment and remain chemically toxic for a prolonged period of time.

### **Pertinent Assessment Findings**

The signs and symptoms exhibited with the toxidrome of DUMBELS [see Patient Presentation – Inclusion Criteria above]

### **Quality Improvement**

#### **Associated NEMESIS Protocol(s) (eProtocol.01)**

9914047—Exposure-Nerve Agents

### **Key Documentation Elements**

- Time to recognize initial signs and symptoms
- Number of repeated doses of atropine required for the secretions diminish and respirations to improve

- Patient reassessments
- Patient responses to therapeutic interventions
- Measures taken to decontaminate the patient
- Measures taken to protect clean environments from contamination

### Performance Measures

- Ability of the EMS system to rapidly locate additional and adequate antidote assets
- Ability of the EMS system to rapidly deploy additional and adequate antidote assets
- Survival rates of victims
- Complication rates from the toxin
- Complication rates from the antidotes
- Long-term clinical sequelae of the victims

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