June 27, 2018

Contingency Medical Countermeasures for Treating Nerve Agent Poisoning

Goal: Nerve agent attacks can overwhelm available resources including pharmaceutical antidote stocks. The guidelines presented here are intended to provide the medical and first responder community with information about contingency pharmaceutical options when conventional therapies are exhausted or preferred formulations or routes of administration are not available for all who require therapy.

Setting: A resource depleted environment **on the scene of the incident or at a health care facility**.

Process: These guidelines represent a subject matter expert (SME) panel consensus of contingency i) anticholinergic medications and ii) benzodiazepine anticonvulsant medications that could be substituted for conventional therapies. A review of the medical literature on the contingency pharmaceutical's efficacy against nerve agent and equivalent effective dosing by contingency routes of administration was performed. The Chemical Integrated Program Team (Chem IPT), an SME-membered federal interagency group addressing chemical defense issues, contributed and approved these guidelines, which align with a position statement by the American College of Medical Toxicology endorsing the consideration of contingency therapies for nerve agent poisoning when conventional therapies are not available (https://www.acmt.net/_Library/Positions/ACMT_Position_Acet.pdf).

The types of contingency pharmaceuticals described here are FDA approved drugs (depending on the manufacturer) AND are currently available in the formulation listed; however, their use as a contingency for the treatment of nerve agent-exposed patients would be considered off-label. Thus, the decision to use these medications and the amount to use must be at the sole discretion of the treating medical provider or medical authority.

Preferred routes of medical countermeasure (MCM) administration typically include intravenous (IV) and intramuscular (including autoinjectors). The IV route is preferred and should be used as soon as possible, especially in critically ill patients. In a resource depleted environment, additional routes of administration include sublingual, inhaled, and intranasal. In many cases, the Chem IPT has endorsed these alternative routes in MCM development criteria due to their speed and ease of administration by responders faced with multiple patients requiring rapid treatment. Dosing information was based on best available evidence from human and animal studies along with pharmacokinetic data. The guidelines represent starting doses and should be titrated to a decrease in respiratory secretions or termination of convulsions. **This information is intended to augment decision making in a low resource state when faced with patients who are deemed in need of treatment for nerve agent toxicity. Conventional therapies should be administered if adequate supplies are available.** In the event that these contingency MCMs are also insufficient, crisis standards of care may need to be applied.[1]

Expected Actions:

- Utilize conventional therapies as long as they are available; consider adoption of contingency options when conventional therapies are exhausted.
- Prioritize treatment to control respiratory secretions and ensure seizure termination.
- Triage to definitive acute medical care based on symptom severity and clinical necessity.

[1] Institute of Medicine of the National Academies (2012). Crisis standards of care: A systems framework for catastrophic disaster response. https://tinyurl.com/y95r4le3

Adult Nerve Agent Medical Countermeasure (MCM) Treatment

Conventional MCMs

Contingency MCMs

SL – sublingual; **IN** – intranasal (dose is divided into each nare using an intranasal mucosal atomization device); **IO** – intraosseous; **AI** - autoinjector; **IV** - intravenous; **IM** - intramuscular
Ophth – Ophthalmic (eye drop) preparations; **gtt** - drops

Signs and Symptoms of Nerve Agent Exposure

Mild

1 DuoDote AI

OR

Atropine 1% Ophth 5gtt SL
Or
Cyclopentolate 1% Ophth 20gtt SL
Or
Glycopyrrolate 0.4mg IV/IM/IO

Moderate

2 DuoDote AI
Or
1 DuoDote AI And 1 AtroPen 2mg AI

OR

Atropine 1% Ophth 10gtt SL Or
Cyclopentolate 1% Ophth 40gtt SL Or
Glycopyrrolate 1mg IV/IM/IO

AND
Ipratropium inhaler 4-6 puffs
OR
Tiotropium inhaler – 2 capsules

If present

Severe

3 DuoDote AI
AND
AtroPen 2mg AI q 3-5 min
AND
Diazepam 10mg AI or IV/IM/IO

OR

Atropine 1% Ophth 20gtt SL Or
Cyclopentolate 1% Ophth 80gtt SL Or
Glycopyrrolate 2mg IV/IM/IO

AND
Pralidoxime 2g IV/IM/IO
AND
Diazepam 10mg AI or IV/IM/IO or
Midazolam 10mg IV/IM/IO

Seizures

Diazepam 10mg AI or IV/IM/IO
Or
Midazolam 10mg IV/IM/IO

OR

Midazolam 10mg IN
Or
Lorazepam 6mg IV/IM/IO/IN

Equivalent Dosing of Conventional Therapies
DuoDote AI: Atropine 2mg IV/IM/IO
AND Pralidoxime 600mg IV/IM/IO
AtroPen 2 mg: Atropine 2mg IV/IM/IO

Additional Dosing
Severe – atropine 2mg IV/IM/IO or contingency agent and route q 3-5 min until resolution of bronchorrhea; adequate ventilation

Additional Dosing
Ongoing Seizures – Diazepam or Midazolam 10mg IV/IM/IO or contingency agent and route q 3-5 min until seizure termination

Pharmaceutical Interchangeable Products
DuoDote™ = Mark 1 Kit = ATNAA
AtroPen™ = Rafa Atropine AI

Conversions – Atropine 1% and Cyclopentolate 1% Ophthalmic (Ophth) Solutions
1ml = 20gtt
1% solution = 10mg/ml

Definitions

Mild: *No respiratory symptoms, but rhinorrhea, blurred vision, miosis, eye pain, lacrimation, salivation, cough, nausea, vomiting, fasciculations*
Moderate: *Respiratory symptoms of shortness of breath, chest tightness, wheezing, dyspnea +/- non-respiratory symptoms of mild category*
Severe: *Bronchorrhea, severe dyspnea, respiratory arrest, urination, defecation, muscle weakness, paralysis, altered mental status, coma*
*Seizures are possible with all exposures but typically in the moderate or severe category**
* Alternative MCM allows for dose flexibility but should be titrated to respiratory secretions (anticholinergics) and seizure termination (benzodiazepines).

Symptom classification and standard MCM Guidelines adapted from Unites States Army Medical Research Institute of Chemical Defense (USAMRICD) "Medical Management of Chemical Casualties" and Advanced HazMat Life Support (AHLS) "Insecticide Poisoning" Table 18-1 Classification of OP Induced Signs & Symptoms

Pediatric Nerve Agent Medical Countermeasure (MCM) Treatment

SL – sublingual; **IN** – intranasal (dose is divided into each nare using intranasal mucosal atomization device); **IO** – intraosseous; **AI** – autoinjector; **IV** – intravenous; **IM** – intramuscular **Ophth** – Ophthalmic (eye drop) preparations; **gtt** - drops

Definition of Pediatric Patients

Less than 18 years old AND ideal body weight ≤ 40kg
If ideal body weight > 40kg, adult dosing is more appropriate

Conventional MCMs | **Contingency MCMs**

Mild

1 DuoDote AI

OR

Atropine 1% Ophth 5gtt SL
Or
Cyclopentolate 1% Ophth 20gtt SL
Or
Glycopyrrolate 0.4mg IV/IM/IO

Moderate

2 DuoDote AI
Or
1 DuoDote AI and
1 AtroPen 2mg AI

OR

Atropine 1% Ophth 10gtt SL Or
Cyclopentolate 1% Ophth 40gtt SL Or
Glycopyrrolate 0.8mg IV/IM/IO

And
Ipratropium inhaler 4-6 puffs
Or
Tiotropium inhaler – 2 capsules

Severe

3 DuoDote AI AND AtroPen 2mg AI
q 3-5 minutes AND
Diazepam 10mg AI/IV/IM/IO (>40kg)
IF LESS THAN 40 kg
Midazolam IV/IM/IO <13kg – 70mcg/kg
13-40kg - 5mg
>40kg - 10 mg

OR

Atropine 1% Ophth 20gtt SL Or
Cyclopentolate 1% Ophth 80gtt SL Or
Glycopyrrolate 2mg IV/IM/IO

AND
Pralidoxime 2g IV/IM/IO
AND
Midazolam IV/IM/IO <13kg – 70mcg/kg
13-40kg - 5mg
>40kg - 10mg

→ Additional Dosing
Severe – atropine 2mg IV/IM/IO or contingency agent and route q 3-5 min until resolution of bronchorrhea; adequate ventilation

If present

Seizures

Diazepam (>40kg) 10mg AI or IV/IM/IO or
Midazolam IV/IM/IO <13kg – 70mcg/kg
13-40kg - 5mg
>40kg -10mg

OR

Midazolam 0.2mg/kg IN (Max 10mg)
Or
Lorazepam 0.1mg/kg IN (Max 6mg)
Or
Lorazepam (≥40kg) 6mg IM/IO
(<40kg) 4mg IM/IO

→ Additional Dosing
Ongoing Seizures – Diazepam or Midazolam 10mg IV/IM/IO or contingency agent and route q 3-5 min until seizure termination

Pharmaceutical Interchangeable Products

DuoDote™ = Mark 1 Kit = ATNAA
AtroPen™ = Rafa Atropine AI

Equivalent Dosing of Conventional Therapies

DuoDote AI: Atropine 2mg IV/IM/IO AND Pralidoxime 600mg IV/IM/IO
AtroPen 2mg: Atropine 2mg IV/IM/IO

Conversions – Atropine 1% and Cyclopentolate 1% Ophthalmic (Ophth) Solutions

1ml = 20gtt
1% solution = 10mg/ml

Definitions

Mild: *No respiratory symptoms, but rhinorrhea, blurred vision, miosis, eye pain, lacrimation, salivation, cough, nausea, vomiting, fasciculations*
Moderate: *Respiratory symptoms of shortness of breath, chest tightness, wheezing, dyspnea +/- non-respiratory symptoms of mild category*
Severe: *Bronchorrhea, severe dyspnea, respiratory arrest, urination, defecation, muscle weakness, paralysis, altered mental status, coma*

- Seizures are possible with all exposures but typically in the moderate or severe category*
- Caveat: Scant literature exists on auto-injectors in pediatrics and listed dosing reflects those recommendations. Alternative MCM allows for dose flexibility but should be titrated to respiratory secretions (anticholinergics) and seizure termination (benzodiazepines).

Symptom classification and standard MCM Guidelines adapted from Unites States Army Medical Research Institute of Chemical Defense (USAMRICD) "Medical Management of Chemical Casualties" and Advanced HazMat Life Support (AHLS) "Insecticide Poisoning" Table 18-1 Classification of OP Induced Signs & Symptoms