Agency for Toxic Substances and Disease Registry
Case Studies in Environmental Medicine
Cholinesterase Inhibitors: Including Pesticides and Chemical Warfare Nerve Agents

Course: WB1102
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Key Concepts	• Cholinesterase inhibitors are a class of compounds that includes chemical warfare nerve agents and certain insecticides. • Fatalities occur mainly due to effects on respiration due depression of respiratory drive, paralysis of muscles of respiration, bronchoconstriction, and airway obstruction from profuse respiratory tract secretions. • Treatment includes the use of atropine, 2-PAM, diazepam, and aggressive supportive care.
About This and Other Case Studies in Environmental Medicine	This educational case study document is one in a series of self-instructional publications designed to increase the primary care provider's knowledge of hazardous substances in the environment and to promote the adoption of medical practices that aid in the evaluation and care of potentially exposed patients. The complete series of *Case Studies in Environmental Medicine* is located on the ATSDR Web site at URL: www.atsdr.cdc.gov/csem/. In addition, the downloadable PDF version of this educational series and other environmental medicine materials provides content in an electronic, printable format, especially for those who may lack adequate Internet service.
How to Apply for and Receive Continuing Education Credit	See Internet address www2.cdc.gov/atsdrce/ for more information about continuing medical education credits, continuing nursing education credits, and other continuing education units.
Acknowledgements	We gratefully acknowledge the work that the medical writers, editors, and reviewers have provided to produce this educational resource. Listed below are those who have contributed to development of this version of the *Case Study in Environmental Medicine*. **Please Note:** Each content expert for this case study has indicated that there is no conflict of interest to disclose that would bias the case study content. **ATSDR Authors:** Erik Auf der Heide, MD **ATSDR Planners:** Valerie J. Curry, MS; John Doyle, MPA; Bruce J. Fowler, Ph.D.; Kimberly Gehle, MD; Sharon L. Hall, Ph.D.; Michael Hatcher, DrPH; Kimberly Jenkins, BA; Ronald T. Jolly; Delene Roberts, MSA; Brian Tencza, MS. **ATSDR Commenters:** Susan Gorman, PharmD, SB; Paul Joe, M.D.; Nickolette Roney, BA **Peer Reviewers:** Alan H. Hall, M.D., Toxicology Consulting and Medical Translating Services, Inc. (TCMTS, Inc.), P.O. Box 184**,** Mile 5.0 Pass Creek Road, Elk Mountain, WY 82324; Sheldon L. Wagner, MD, Professor of Clinical Toxicology, Oregon State University, Emeritus, Corvallis, Oregon 97331-2106

Disclaimer	The state of knowledge regarding the treatment of patients potentially exposed to hazardous substances in the environment is constantly evolving and is often uncertain. In this educational monograph, ATSDR has made diligent effort to ensure the accuracy and currency of the information presented, but makes no claim that the document comprehensively addresses all possible situations related to this substance. This monograph is intended as an educational resource for physicians and other health professionals in assessing the condition and managing the treatment of patients potentially exposed to hazardous substances. It is not, however, a substitute for the professional judgment of a health care provider. The document must be interpreted in light of specific information regarding the patient and in conjunction with other sources of authority. Use of trade names and commercial sources is for identification only and does not imply endorsement by the Agency for Toxic Substances and Disease Registry or the U.S. Department of Health and Human Services.
	**U.S. Department of Health and Human Services** **Agency for Toxic Substances and Disease Registry** **Division of Toxicology and Environmental Medicine** **Environmental Medicine and Educational Services Branch**

How to Use This Course

Introduction	The goal of *Case Studies in Environmental Medicine* (CSEM) is to increase the primary care provider's knowledge of hazardous substances in the environment and to help in evaluation and treating of potentially exposed patients. This CSEM focuses on cholinesterase inhibitors.
Available Versions	Two versions of the *Cholinesterase Inhibitors, Including Pesticides and Chemical Warfare Nerve Agents* CSEM are available • The HTML version http://www.atsdr.cdc.gov/csem/cholinesterase/ provides content through the Internet. • The downloadable PDF version provides content in an electronic, printable format, especially for those who may lack adequate Internet service. The HTML version offers interactive exercises and prescriptive feedback to the user.
Instructions	To make the most effective use of this course, we recommend that you: • Take the Initial Check to assess your current knowledge about cholinesterase inhibitors. • Read the title, learning objectives, text, and key points in each section. • Complete the progress check exercises at the end of each section and check your answers. • Complete and submit your assessment and posttest responses online if you wish to obtain continuing education credit. Continuing education certificates can be printed immediately upon completion.
Optional Reading	Optional reading sections cover supplemental and advanced topics. Post-test questions do not cover material in these sections.
Instructional Format	This course is designed to help you learn efficiently. Topics are clearly labeled so that you can skip sections or quickly scan sections you are already familiar with. This labeling will also allow you to use this training material as a handy reference. To help you identify and absorb important content quickly, each section is structured as follows:

Section Element	Purpose
Title	Serves as a "focus question" that you should be able to answer after completing the section.
Learning Objectives	Describes specific content addressed in each section and focuses your attention on important points.
Text	Provides the information you need to answer the focus question(s) and achieve the learning objectives
Key Points	Highlights important issues and helps you review.
Progress Check exercises	Enables you to test yourself to determine whether you have mastered the learning objectives.
Progress Check answers	Provides feedback to ensure you understand the content and can locate information in the text.

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Learning Objectives Upon completion of the Cholinesterase Inhibitors CSEM, you should be able to:

Topic	Objectives
Community preparedness	• Identify key community agencies that should be involved in planning, training, and exercises for hazardous materials emergencies and disasters, such as those due to exposure to cholinesterase inhibitors • Describe the consequences that result when many patients exposed to hazardous materials, such as cholinesterase inhibitors, transport themselves to the hospital.
What are cholinesterase inhibitors?	• Describe how cholinesterase inhibitors, including organophosphorus compounds (*e.g.,* pesticides, nerve agents) and carbamates block the ability of acetylcholinesterase to break down acetylcholine.
What types of pathology do cholinesterase inhibitors cause?	• Identify the 4 major types of pathology caused by cholinesterase inhibitors
What is the cholinergic toxidrome?	• Describe what causes the cholinergic toxidrome. • Identify generally where cholinergic receptors are found. • Identify the differences between nicotinic and muscarinic receptors. • Identify why excessive levels of acetylcholine (the cholinergic toxidrome) cause different signs and symptoms depending on whether cholinergic receptors involved are of the muscarinic or nicotinic type.

Clinical findings are due to a mixture of nicotinic and muscarinic effects	• Describe factors that account for variation in the clinical presentation of cholinesterase toxicity. • Describe the CNS effects cholinesterase inhibitor toxicity. • Describe what is known about the nicotinic and muscarinic effects of cholinesterase toxicity on the central nervous system. • Identify 4 factors contributing to respiratory failure and death in cases of cholinesterase inhibitor toxicity.
Effects on routine laboratory tests	• Describe what routine laboratory tests can be altered by acute cholinesterase inhibitor toxicity.
Differential diagnosis	• Identify other medical conditions that can be mimicked by the cholinergic toxidrome.
Signs and symptoms: Differences in pediatric cases	• Identify how the in clinical presentation in pediatric cases of the cholinergic toxidrome differs from that in adults.
Who is at risk for exposure? The exposure history	• Identify potential sources of exposure to cholinesterase inhibitors. • Identify the important elements to include in an exposure history when evaluating patients who might be suffering from cholinesterase inhibitor toxicity.
RBC and serum cholinesterase levels	• Describe the usefulness and limitations of laboratory analysis of RBC and serum cholinesterase levels.
Direct measurement of cholinesterase inhibitors and their metabolic byproducts	• Describe the usefulness and limitations of laboratory analysis for the presence of cholinesterase inhibitors themselves and their breakdown products in biological specimens.
Management Strategy 1: Prevention of secondary exposure	• Describe 5 key strategies for preventing secondary exposure from patients contaminated with cholinesterase inhibitors.
Management strategy 2: Supportive care	• Identify the most important organ system requiring supportive care in patients suffering from the cholinergic toxidrome.

Management strategy 3: Medications - Atropine	Identify • The mechanism by which atropine counters the effects of the cholinergic toxidrome. • Findings against which to titrate atropine dosage. • The preferred routes of administration of atropine. • The type of cholinesterase inhibitor toxicity that may require extremely high doses of atropine.
Management strategy 3: Medications - 2-PAM	Describe • How 2-PAM works as an antidote. • How 2-PAM influences the body's response to atropine and vice-versa. • What "aging" is, as it relates to 2-PAM, and how the process can affect response to treatment. • Situations that delay the onset of toxicity and aging of cholinesterase inhibitors. • Reasons for treatment failure with 2-PAM. • The recommendations for use of 2-PAM in carbamate poisoning.
Management strategy 3: Medications - Diazepam	Describe • Why seizure prevention and control is important in the management of the cholinergic toxidrome. • The difference in the risk of seizures between adults and pediatric cases of the cholinergic toxidrome.
Syrup of ipecac, gastric lavage, cathartics, and activated charcoal	• Describe the roles of the following treatment modalities in the management of poisoning due to cholinesterase inhibitors: o Syrup of ipecac. o Gastric lavage. o Cathartics. o Activated charcoal.
Public health and medico-legal issues	• Describe the importance of notifying public health authorities and other emergency response agencies in poisonings due to cholinesterase inhibitor.

The intermediate syndrome	Describe the • Clinical findings in the intermediate syndrome. • Significance of the intermediate syndrome in regards to morbidity and mortality due to cholinesterase inhibitor poisoning. • Treatment and prognosis for intermediate syndrome.
Organophosphate-induced delayed neuropathy (OPIDN)	Identify the • Clinical findings in OPIDN compared to the intermediate syndrome. • Available treatments for OPIDN. • Current knowledge about the cause of OPIDN.
Organophosphorus ester-induced chronic neurotoxicity (OPICN)	Describe • Our current level of understanding about the association of OPICN and asymptomatic exposures to cholinesterase inhibitors. • Current treatment options.
Other issues related to cholinesterase inhibitor toxicity	• Describe our current knowledge about the association of cholinesterase inhibitor exposure with o Cancer risks. o Fetal effects. o Gulf War I illness. o Immune system effects.

Initial Check

Instructions	This Initial Check will help you assess your current knowledge and skill level about cholinesterase inhibitors. To take the Initial Check, read the case below, answer the questions that follow, and then compare your answers with the answers provided.
Case Study	You are the attending emergency physician on duty in a 200 bed metropolitan emergency department. While seeing a patient with an ankle injury, you are interrupted by the head nurse. He reports that one of the other nurses has become ill while taking the vital signs of a patient who had just arrived by private vehicle along with five family members with similar symptoms. The patient's complaints included eye pain, dimness of vision, cough and runny nose. The nurse was now suffering from similar symptoms along with dizziness. Shortly thereafter, you are told that another patient has arrived in the back of a pickup truck. He is complaining of eye pain, blurred vision, and is diaphoretic and in severe, acute respiratory distress. As his friends were helping him to the emergency department entrance, the patient suffered a grand mal seizure. At this point, a call comes over the paramedic radio system reporting that units are responding to a multiple-victim vehicle crash involving hazardous materials. You note from the radio report that yours is the closest hospital to the scene. The head nurse tells you that it sounds like the same location (six blocks from the hospital) from which the first eye-pain patients came. He suggests that you might want to initiate the emergency department decontamination and disaster plans.
Initial Check Questions	1. What aspects of this situation suggest toxic exposure to a cholinesterase inhibitor? 2. Who needs to be notified about this incident? 3. What supplies and equipment will you need immediately to deal with this incident? 4. How will most patients from this incident get to the hospital? 5. What hospital(s) is/are likely to receive most of the patients from the crash site? 6. What are the major classifications of signs and symptoms characteristic of cholinesterase inhibitor poisoning? 7. What is the pathophysiology underlying the clinical findings in cholinesterase inhibitor poisoning? 8. What laboratory tests are most helpful in guiding the emergency treatment of acute cholinesterase inhibitor toxicity? 9. What are the major treatment strategies recommended in acute cholinesterase inhibitor poisoning? 10. What are the three major delayed adverse effects that can follow recovery from the acute cholinesterase toxicity? 11. What is the usual cause of death from acute cholinesterase inhibitor poisoning?

Answers

1. **What aspects of this situation suggest toxic exposure to a cholinesterase inhibitor?**
The clinical findings of eye pain, blurred or dim vision, respiratory distress, diaphoresis and seizures are all consistent with cholinesterase inhibitor poisoning. Although the nurse may not have noticed it, the patients probably also had constricted pupils.

The information for this answer comes from Part 2, sections 2 and 3.

2. **Who needs to be notified about this incident?**
The 911 dispatcher needs to be notified, so that she can relay the information to ambulances and other emergency personnel at the scene. Other hospitals should be notified, so they can hopefully have some lead time to don personal protective gear and set up decontamination equipment before they start receiving casualties. The chief, in-house, acting administrator needs to be notified so that the hospital disaster plan can be activated. The poison center should be notified, since it may be receiving calls about the incident.

The information for this answer comes from Part 1. Community Preparedness for Mass Casualty Events Involving Cholinesterase Inhibitors.

3. **What supplies and equipment will you need immediately to deal with this incident?**
The emergency department will need appropriate personal protective equipment, decontamination equipment (chemically-resistant suites with hoods, booties, and two-layers of gloves, full-face air-supplied or filtered respirators with appropriate cartridge filter), antidotes (atropine, 2-PAM, and diazepam), airway equipment, and ventilators.

The information for this answer comes from Part 4, Section 11. Management of the Cholinergic Toxidrome.

4. **How will most patients from this incident get to the hospital?**
Experience has shown that many casualties from disasters and hazardous materials incidents are transported by private vehicle, or if the hospital is very close (as it is in this case) even on foot.

The information for this answer comes from Part 1. Community Preparedness for Mass Casualty Events Involving Cholinesterase Inhibitors.

5. **What hospital(s) are likely to receive most of the patients from the crash site?**
Your hospital is likely to receive most of the casualties, because it is the closest to the disaster. In large scale emergencies or disasters, most casualties are transported to the closest hospitals.

The information for this answer comes from Part 1.

6. What are the major classifications of signs and symptoms characteristic of cholinesterase inhibitor poisoning?

Over stimulation of exocrine glands: Salivation, sweating, lacrimation, rhinorrhea, bronchorrhea.

Smooth muscle stimulation: bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea), urination, constriction of pupils.

Over stimulation of skeletal muscle with subsequent fatigue: fasciculations, myoclonic jerks, weakness, flaccid paralysis

CNS effects: Anxiety, restlessness, irritability, headache, and insomnia with nightmares, emotional lability, depression, delirium, seizures, and coma.

The information for this answer comes from Part 2, sections 2 and 3.

7. What is the pathophysiology underlying the clinical findings in cholinesterase inhibitor poisoning?

The clinical findings in cholinesterase inhibitor toxicity are due to the inhibition of acetylcholinesterase, resulting in the build up of excessive levels of acetylcholine at neuromuscular junctions and synapses effecting the CNS, skeletal muscles, and smooth muscles and exocrine glands.

The information for this answer comes from Part 2. What are cholinesterase inhibitors?

8. What laboratory tests are most helpful in guiding the emergency treatment of acute cholinesterase inhibitor toxicity?

While laboratory tests can be used to estimate the exposure to cholinesterase inhibitors (cholinesterase levels and direct measurement of cholinesterase inhibitors and their metabolites), they are of limited use and rarely available in time to guide emergency treatment. Initial treatment of life-threatening poisoning should instead be based on clinical findings.

The information for this answer comes from Section 10. Laboratory Assessment of the Cholinergic Toxidrome: Red Blood Cell (RBC) and Serum Cholinesterase and Direct Measurement of Cholinesterase Inhibitors and Their Metabolic Byproducts.

9. What are the major treatment strategies recommended in acute cholinesterase inhibitor poisoning?

- Limiting further exposure of the patient by removing clothing and carrying out decontamination
- Prevention of secondary contamination of others

- Aggressive supportive care (respiratory care in particular)
- Antidotal medications (atropine, 2-PAM, and diazepam)

The information for this answer comes from Section 11.

10. What are the three major delayed adverse effects that can follow recovery from the acute cholinesterase toxicity?

Organophosphate-induced delayed neuropathy (OPIDN) can occur 1-5 weeks after severe poisoning and lead to peripheral neuropathy, with pain, paresthesias, weakness, and paralysis.

Intermediate syndrome can occur after 1-4 days after resolution of acute cholinesterase inhibitor toxicity, leading to potentially lethal respiratory failure from muscle weakness and paralysis.

Organophosphorus ester-induced chronic neurotoxicity (OPICN), also called chronic organophosphate-induced neuropsychiatric disorder (COPIND), consists of persistent findings, such as fatigue, depression, and problems with concentration, abstract reasoning, and fine motor coordination attributed to cholinesterase inhibitor poisoning. Some have argued that these findings are consistent with CNS damage from hypoxia and seizures, and may not be a specific organophosphorus toxic effect.

The information for this answer comes from Parts 5, 6 and 7.

11. What is the usual cause of death from acute cholinesterase inhibitor toxicity?

Respiratory failure from central respiratory depression, paralysis of respiratory muscles, severe bronchospasm, and excessive respiratory secretions (bronchorrhea).

The information for this answer comes from Section 11.

Part 1: Community Preparedness for Mass Casualty Events Involving Cholinesterase Inhibitors

Learning Objectives

Upon completion of this portion of the case study, you should be able to:

- Identify key community agencies that should be involved in planning, training, and exercises for hazardous materials emergencies and disasters, such as those due to exposure to cholinesterase inhibitors.
- Describe the consequences that result when many patients exposed to hazardous materials, such as cholinesterase inhibitors, transport themselves to the hospital.

Introduction

As the case presentation illustrates, cholinesterase inhibitors can be involved in mass casualty events. A notable example was the Sarin attack on the Tokyo subway in 1995. The ability to provide good clinical care, especially when multiple casualties are involved, requires good organizational management and planning activities at both the institutional and community level.

MISCONCEPTION: Each hospital should develop a plan for dealing with cholinesterase inhibitor exposed patients.

REALITY: Effective management of these cases requires planning, training, emergency communications, and coordination *at the community level*.

Need for Community Level Planning, Training, and Drills

The response to hazardous materials emergencies and disasters requires planning, training, exercising, and coordination *at the community level*. (Auf der Heide 1989; Auf der Heide 2002; Auf der Heide 2006)

At a minimum, the following organizations should be involved:

- All area hospitals.
- All area emergency medical services (*e.g.,* ambulance) agencies and providers.
- Emergency management/disaster offices.
- Environmental protection offices.
- Fire departments.
- Law enforcement agencies (including FBI).
- Metropolitan Medical Response Systems (MMRSs). (For more information go to http://mmrs.fema.gov).
- Public health agencies.
- The Local Emergency Planning Committee (LEPC) required under the Superfund Amendments and Reauthorization Act (SARA) Title III laws for hazmat preparedness. For more information go to http://yosemite.epa.gov/oswer/ceppoweb.nsf/content/epcraOverview.htm
- The poison center

Coordination of Community Personnel

Response issues that require community-wide coordination and communication include the need for someone that will coordinate personnel responsible for:

- Evacuating/sheltering-in-place of community medical facilities (if required).
- Notifying hospitals of an incident involving hazardous materials (such as nerve agents or pesticides).
- Field medical and public health response units.
- Deciding when to issue an order for the public to evacuate or shelter-in-place.
- Distributing of large amounts of antidotes among the area medical facilities (if needed).
- Dissemination of information (*e.g.,* via the mass media) that will help the public protect itself.
- Tracking and releasing of the information needed to address massive inquiries about the missing.

The Importance of Evidence-Based Planning

Dealing with victims exposed to hazardous materials, such as cholinesterase inhibitors, requires effective planning at both the institutional and community level. However, the effectiveness of planning is only as good as the assumptions upon which it is based.

While the existing empirical literature on medical responses to hazardous material emergencies and disasters is limited, both in its extent and quality, there are some important findings relevant to planning. A number of these are not specific to, but are applicable in, cases of cholinesterase inhibitor exposure. These are discussed below.

MISCONCEPTION: Hospitals should work with local fire departments and EMS providers to encourage them to decontaminate patients contaminated with cholinesterase inhibitors in the field before transporting them to hospitals.

REALITY: Available studies indicate that many chemically exposed patients arrive unannounced at the closest hospitals after being transported by themselves or bystanders --- effectively bypassing the EMS system and any field attempts at decontamination. This is true in routine emergencies as well as in disasters. Therefore, *every* hospital must be prepared to decontaminate casualties, and to do so with little or no advanced warning.

Patient Self-Transport

While it may be assumed that patients will enter the hospital by way of the local emergency medical services system, often many patients will get to the hospital by their own means. (Geller, Singleton *et al.* 2001; Vogt and Sorensen 2002; U.S. Occupational Safety and Health Administration 2005; Okumura, Suzuki *et al.* 1998) This pattern is common in disasters as well (Murakami 2000; Auf der Heide 2006)

As a result:

- Patients may arrive without notice. (Auf der Heide 2006)
- Patients may arrive without having been triaged. (Auf der Heide 2006; Okumura, Suzuki *et al.* 1998)
- Patients may be placed in an exam room before it is discovered that they have been exposed to a hazardous substance. (Lambert 1996;

	Geller, Singleton *et al.* 2001) • Patients may arrive without having been decontaminated, and hospital staff may become secondarily contaminated. (Lavoie, Coomes *et al.* 1992; Nozaki and Aikawa 1995; Okudera, Morita *et al.* 1997; Trutt and Oster 1999; Geller, Singleton *et al.* 2001; Horton, Berkowitz *et al.* 2003; Okumura, Suzuki *et al.* 1998) • Patients may tend to converge on the closest or most locally renowned hospitals. (Auf der Heide 2006; Okumura, Suzuki *et al.* 1998) • Timely information on the chemical(s) to which they have been exposed may be lacking.
Planning Implications of Self-Transport	Hospitals may be the first emergency response organizations to learn of an incident involving chemically contaminated casualties. They need to see to it that others are also notified. For example, the 911 dispatcher needs to be notified, so that she can relay the information to ambulances and other emergency personnel at the scene. Other hospitals should be notified, so they can hopefully have some lead time to don personal protective gear and set up decontamination equipment before they start receiving casualties. The chief, in-house, acting administrator needs to be notified so that the hospital disaster plan can be activated. The poison center should be notified, since it may be receiving calls about the incident. Hospitals may have to deal with contaminated casualties before they have had time to don personal protective equipment or set up decontamination showers and equipment. It may be advantageous to have an expedient decontamination procedure until this can be done. One approach may be to have fire hoses and spray nozzles hooked up to a high-capacity, low-pressure, warm-water supply. Then, as a temporizing measure, contaminated victims could be sprayed from a distance without exposing hospital staff to contaminants, or exposing the victims to hypothermia when the weather is inclement. There is an advantage to having decontamination facilities permanently set up, rather than using equipment that must be set up after a patient arrives. Since it is patients, rather than the emergency medical services system, that often determines hospital destination, all hospitals must have the capacity to deal with contaminated casualties.
Key Points	• The response to hazardous materials emergencies and disasters requires planning, training, exercising, and coordination at the community level. This may involve several organizations.

Progress Check

1. Which of the following community emergency response agencies should be involved in planning for disasters such as those involving mass exposures to cholinesterase inhibitors? (Choose **ALL** correct answers.)

   A. All area hospitals.
   B. Public health agencies.
   C. The poison center.
   D. The Local Emergency Planning Committee (LEPC).
   E. None of the above.

   To review relevant content, see "Need for Community Level Planning, Training, and Drills" in this section.

2. Which of the following assumptions form the basis of effective planning for the medical management of patients exposed to and/or contaminated with cholinesterase inhibitors: (Choose **ALL** correct answers.)

   A. Patients will be decontaminated in the field prior to ambulance transport.
   B. Each community should designate a single hospital to receive contaminated casualties.
   C. Ambulances will give advance notice to hospitals about the arrival of contaminated patients.
   D. None of the above.

   To review relevant content, see "The Importance of Evidence-Based Planning" in this section.

Part 2: What are cholinesterase inhibitors?

Learning Objectives

Upon completion of this portion of the case study, you should be able to:

- Identify the chemical responsible for the acute pathology in cholinesterase inhibitor poisoning.
- Describe how cholinesterase inhibitors, including organophosphorus compounds (*e.g.,* pesticides, nerve agents) and carbamates block the ability of acetylcholinesterase to break down acetylcholine.

The Primary Toxic Effect of Cholinesterase Inhibitors

Acetylcholinesterase inhibitors (which, for brevity, we will refer to as cholinesterase inhibitors) are chemicals whose primary toxic effect is to block the normal breakdown of the neurotransmitter, **acetylcholine**. This normal breakdown is shown in **Figure 1** below.

Breakdown of Acetylcholine *(Optional Reading)*

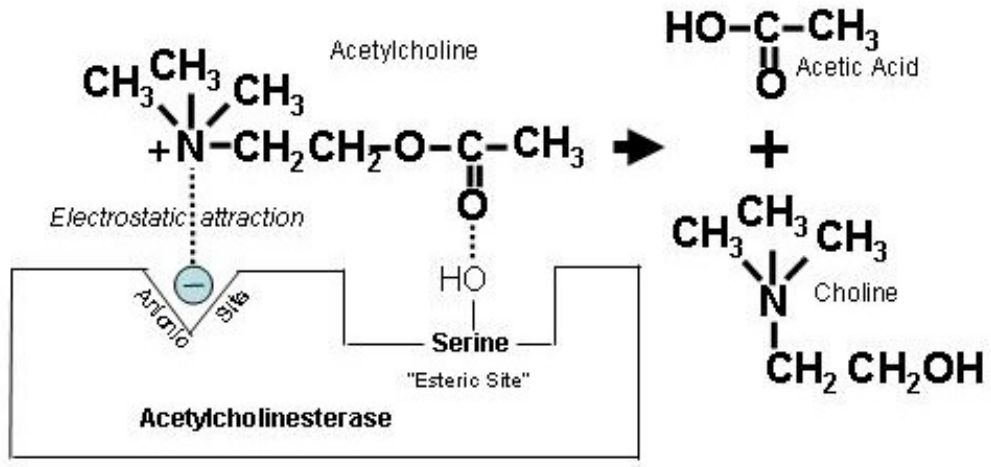


Figure 1. Breakdown of acetylcholine.

Breakdown of Acetylcholine *(Optional Reading)*

They do this by occupying and blocking the site where the neurotransmitter, **acetylcholine**, attaches to the enzyme, **acetylcholinesterase**. If you are interested in the details at the chemical level, see the Optional Reading below.

How Acetylcholine is Blocked *(Optional Reading)*

Figure 2 below shows how a cholinesterase inhibitor (in this case, a nerve agent) attaches to the serine hydroxyl group on acetyl-cholinesterase. This prevents acetylcholine from interacting with the cholinesterase enzyme and being broken down.

δ + Indicates that phosphorus is partially electropositive.

δ – Indicates that oxygen is partially electronegative.

Diagrams modified from Wiener, S. W., and R. S. Hoffman. "Nerve Agents: A Comprehensive Review." *Journal of Intensive Care Medicine* 19, no. 1 (2004): 22-37.

Attraction of Cholinesterase Inhibitor to Acetyl-Cholinesterase ***(Optional Reading)***

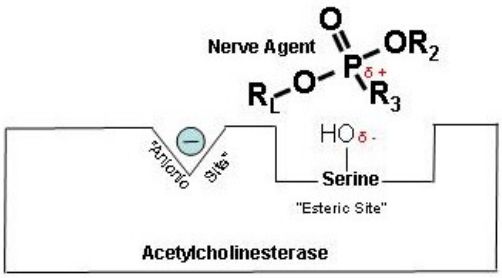


Figure 2. Partially electropositive phosphorus is attracted to partially electronegative serine.

Molecular Bond Changes ***(Optional Reading)***

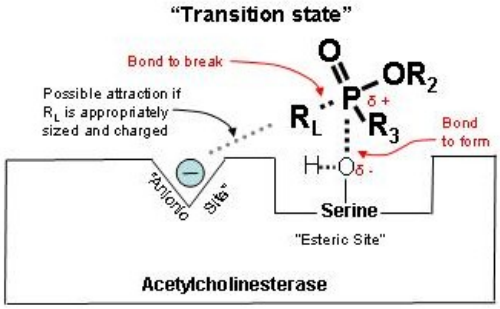


Figure 3. Transition state showing which bonds break and which ones form.

Cholinesterase Inhibitor Attached to Cholinesterase ***(Optional Reading)***

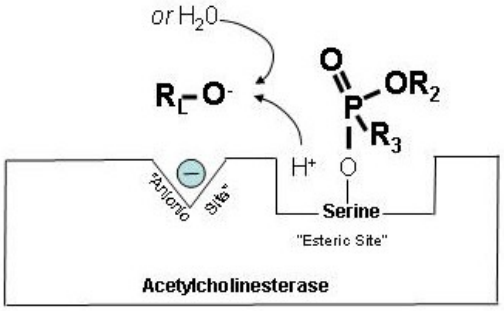


Figure 4. Cholinesterase inhibitor attached to acetylcholinesterase preventing the attachment of acetylcholine.

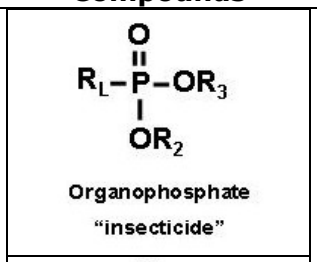
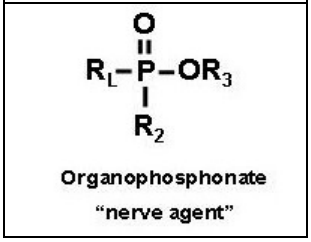
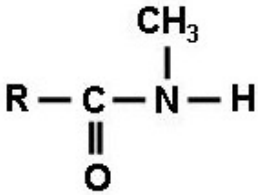
Effects of Blocked Acetylcholine Breakdown ***(Optional Reading)***

This leads to the build up of excessive levels of the neurotransmitter, **acetylcholine**, at the skeletal neuromuscular junction and those synapses where acetylcholine receptors are located.

Thus, the primary manifestations of acute cholinesterase inhibitor toxicity are those of **cholinergic** (neurotransmitter) **hyperactivity**. (Carlton, Simpson *et al.* 1998)

Other Effects of Cholinesterase Inhibitors ***(Optional Reading)***	There are also other delayed and chronic pathological effects of inhibitors of the cholinesterase enzyme which are less well understood. Cholinesterase inhibitors can have effects on a variety of non-cholinesterase enzymes and neurotransmitters, as well. (Somani and Husain 2001) However, the significance of these effects is not well understood.
Review of Definitions	**Acetylcholine**: a chemical neurotransmitter found widely in the body. It triggers the stimulation of post-synaptic nerves, muscles, and exocrine glands. **Acetylcholinesterase** (generally referred to as **cholinesterase**): an enzyme that rapidly breaks down the neurotransmitter, acetylcholine, so that it does not over-stimulate post-synaptic nerves, muscles, and exocrine glands. **Acetylcholinesterase inhibitor** (generally referred to as **cholinesterase inhibitor**): a chemical that binds to the enzyme, cholinesterase, and prevents it from breaking down the neurotransmitter, acetylcholine. With toxic doses, the result is that excessive levels of the acetylcholine build up in the synapses and neuromuscular junctions and glands.

Two Classes of Cholinesterase Inhibitors Two classes of cholinesterase inhibitors are **organophosphorus compounds** and **carbamates**. The key differences are listed in the table below. (Erdman 2004)

	Organophosphorus Compounds	Carbamates
Molecular structure (Ecobichon 1996) **Notes:** "R" denotes a variety of groups that attach to the basic structure. "P=S" of organophosphorus compounds can be substituted for "P=O." "R_L" of organophosphates may attach via an "O" to "P."	 Organophosphate "insecticide"  Organophosphonate "nerve agent"	
Toxicity (Marrs and Dewhurst 2000)	Higher	Lower
Duration of action (Tareg *et al.* 2001)	Longer	Shorter
CNS toxicity (Tareg *et al.* 2001)	More common	Less common

Key Points

- Cholinesterase inhibitor toxicity is due to a decrease in the ability of cholinesterase to breakdown acetylcholine which results in excessively high acetylcholine levels.
- Cholinesterase inhibitors fall into two classes, organophosphorus compounds, and carbamates. The former are generally have higher toxicity, longer duration of action and more commonly cause CNS toxicity.

Progress Check

3. Cholinesterase inhibitor toxicity is due to: (Choose **ALL** correct answers.)

   A. Excessive levels of the enzyme acetylcholinesterase.
   B. Depressed activity of the enzyme acetylcholinesterase.
   C. Excessive levels of the neurotransmitter acetylcholine.
   D. Depressed levels of the neurotransmitter acetylcholine.
   E. None of the above.

   To review relevant content, see "Primary Toxic Effects of Cholinesterase Inhibitors" in this section.

4. Which of the following are true about organophosphates? (Choose **ALL** correct answers.)

   A. They include pesticides.
   B. They include nerve agents.
   C. They are less toxic than carbamates.
   D. They have a longer duration of action than carbamates.
   E. None of the above.

   To review relevant content, see "Two Classes of Cholinesterase Inhibitors" in this section.

5. Cholinesterase inhibitors block the ability of acetylcholinesterase to break down acetylcholine by? (choose the **ONE** best answer.)

   A. Occupying the binding site on cholinesterase to which the acetylcholine would attach.
   B. Preventing the release of acetylcholine from its attachment on cholinesterase.
   C. Attaching to acetylcholine which prevents its attachment to cholinesterase.
   D. None of the above.

   To review relevant content, see "Cholinesterase Inhibitors Block The Normal Breakdown of Acetylcholine" in this section.

Part 3: What types of pathology do cholinesterase inhibitors cause?

Learning Objectives

Upon completion of this portion of the case study, you should be able to:

- Identify the 4 major types of pathology caused by cholinesterase inhibitors.

Categories of Pathological Effects

We have discussed the mechanism behind one form of pathology caused by cholinesterase inhibitors, namely, the build up of acetylcholine. For purposes of our discussion in the Case Study, we will refer to this as the **cholinergic toxidrome**. However, there are 3 other distinct syndromes associated with exposure to these toxins the pathology of which is less well understood. (Erdman 2004) Each of which will be described in this case study.

Category	Description	Where Discussed
Cholinergic toxidrome	Clinical findings due to excessive buildup of acetylcholine. (Hack and Hoffman 2004)	See Part 4
Intermediate syndrome	Delayed neuromuscular dysfunction occurring 24-96 hours after a significant, and usually severe, case of poisoning that usually resolves spontaneously within 1-2 weeks. (Karalliedde and Senanayake 1989; Clark 2002; Erdman 2004)	See Part 5
Organophosphate-induced delayed neuropathy (OPIDN)	Delayed neuropathy of unknown cause with onset occurring 1-5 weeks after recovery from acute cholinergic toxidrome. (Erdman 2004) ; (Jamal 1997; Clegg and van Gemert 1999; Jokanovic, Stukalov *et al.* 2002) Milder cases can recover fully; severe cases can result in permanent disability. (Jokanovic, Stukalov *et al.* 2002)	See Part 6
Organophosphorus ester-induced chronic neurotoxicity (OPICN)	Chronic neurotoxicity that lasts for weeks to years after acute exposure. (Abou-Donia 2003)	See Part 7

Key Points

- There are four pathological conditions attributed to cholinesterase inhibitor exposure
  - The cholinergic toxidrome.
  - The intermediate syndrome.
  - Organophosphate-induced delayed neuropathy (OPIDN).
  - Organophosphorus ester-induced chronic neurotoxicity (OPICN).

Progress Check

6. Which condition(s) consist of neuropathy characteristically occurring 1-5 weeks after recovery from the acute cholinergic toxidrome? (Choose **ALL** correct answers.)

   A. Cholinergic toxidrome.
   B. Intermediate syndrome.
   C. Organophosphate-induced delayed neuropathy (OPIDN).
   D. Organophosphorus ester-induced chronic neurotoxicity (OPICN).
   E. None of the above.

   To review relevant content, see "Categories of Pathological Effects" in this section.

7. Which condition(s) result(s) in chronic neurological effects that characteristically persist for years? (Choose **ALL** correct answers.)

   A. Cholinergic toxidrome.
   B. Intermediate syndrome.
   C. Organophosphate-induced delayed neuropathy (OPIDN).
   D. Organophosphorus ester-induced chronic neurotoxicity (OPICN).
   E. None of the above.

   To review relevant content, see "Categories of Pathological Effects" in this section.

Part 4: The Cholinergic Toxidrome

Section 1: What is the Cholinergic Toxidrome?

Learning Objectives	Upon completion of this section, you should be able to: • Describe what causes the cholinergic toxidrome. • Identify generally where cholinergic receptors are found. • Identify the differences between nicotinic and muscarinic receptors. • Identify why excessive levels of acetylcholine (the cholinergic toxidrome) cause different signs and symptoms depending on whether cholinergic receptors involved are of the muscarinic or nicotinic type.
Introduction	The cholinergic toxidrome represents the acute phase of cholinesterase inhibitor poisoning. It results from the accumulation of excessive levels of acetylcholine in the synapses, glands, smooth muscles, and motor end plates where cholinergic receptors are found. Thus, the pathology of the cholinergic toxidrome (and the clinical picture that results) can best be understood with knowledge of the types of acetylcholine receptors, where they are located, and what physiological processes they modulate.
Types of Cholinergic Receptors	There are 2 main types of cholinergic receptors, **nicotinic** and **muscarinic**, so named because their effects are similar to those of nicotine and muscarine. The **nicotinic** and **muscarinic** receptors: • Are present in different anatomical locations. • Have different functions. • Have different mechanisms by which they trigger signal transmission. (Erdman 2004)
Mixed Nicotinic and Muscarinic Effects	In any given case, the patient's signs and symptoms may vary depending on the balance between sometimes apposing nicotinic and muscarinic effects.
Summary Diagram of Signs and Symptoms	Signs and symptoms of acetyl cholinesterase inhibitors --- and their relationship to **nicotinic** and **muscarinic** receptors --- are summarized in **Figure 5** below. (Gershon and Shaw 1961; du Toit, Muller *et al.* 1981; Lotti 1992; Okumura, Takasu *et al.* 1996; Sidell 1997; Yokoyama, Araki *et al.* 1998; Reigart and Roberts 1999; Tareg *et al.* 2001; Erdman 2004) It is provided here, so that the reader can refer back to this figure as the topic is covered in further detail.

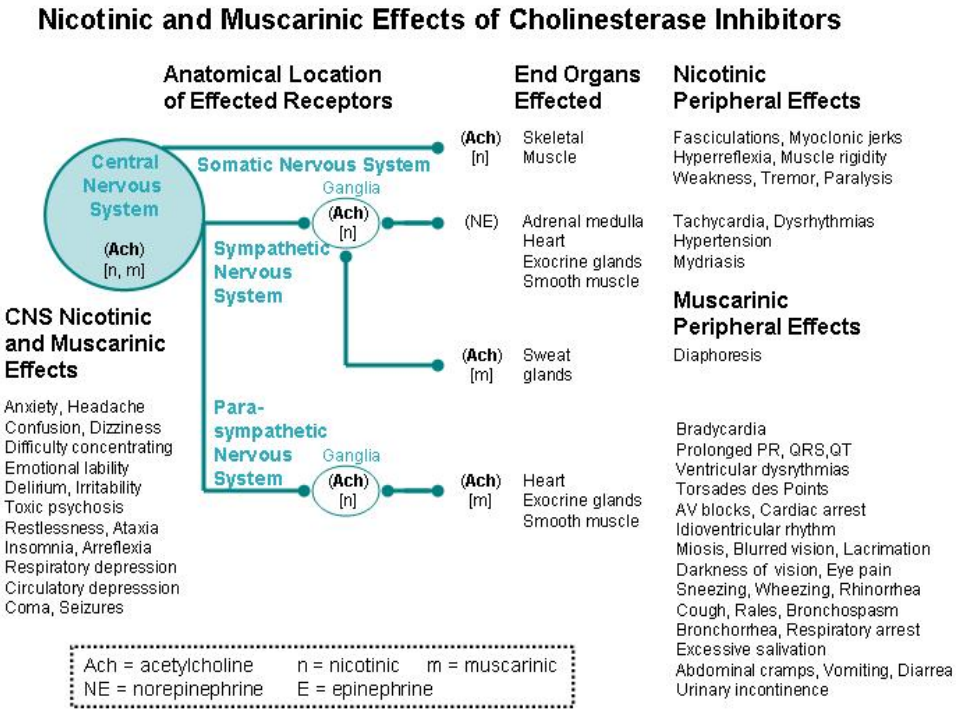


Figure 5. Summary diagram showing where nicotinic and muscarinic receptors are found. Refer back to this when reading the following sections.

Nicotinic vs. Muscarinic Effects	The exact signs and symptoms found in any given individual with cholinesterase toxicity vary depending on the balance of nicotinic and muscarinic stimulation.

Key Points	• The cholinergic toxidrome reflects the acute phase of acetylcholinesterase poisoning.
	• It is the result of inhibition of the enzyme acetylcholinesterase which normally breaks down the neurotransmitter, acetylcholine. The end result is the build up of excessive levels of the neurotransmitter.
	• Symptoms are due to the effects of excess acetylcholine on nicotinic and muscarinic acetylcholine receptors in the CNS, at neuromuscular junctions, and in the sympathetic, and parasympathetic nervous systems.
	• Nicotinic and muscarinic receptors have different
	  o Functions.
	  o Locations.
	  o Physiology.
	  o Structure.

Progress Check

8. Nicotinic and muscarinic receptors: (Choose **ALL** correct answers.)

   A. Are both acetylcholine receptors.
   B. Have the same structure.
   C. Have different physiology.
   D. Have different functions.
   E. None of the above.

   To review relevant content, see "Types of Cholinergic Receptors" in this section.

9. What causes the cholinergic toxidrome? (Choose **ALL** correct answers.)

   A. Elevated levels of acetylcholinesterase.
   B. Elevated levels of acetylcholine.
   C. Acetylcholine deficiency.
   D. None of the above.

   To review relevant content, see "Introduction" in this section.

10. Cholinergic receptors are found in which of the following locations? (Choose **ALL** correct answers.)

    A. The central nervous system.
    B. The sympathetic nervous system.
    C. The parasympathetic nervous system.
    D. The skeletal neuromuscular junctions.
    E. None of the above.

    *To review relevant content, see **Figure 5** in this section.*

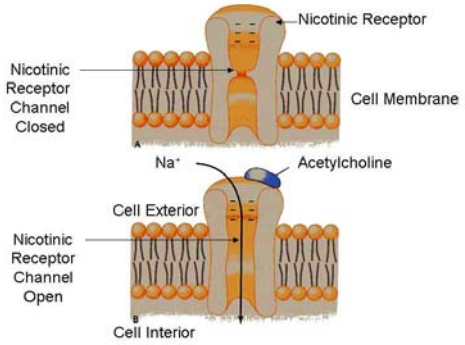
11. Why do excessive levels of acetylcholine ("The cholinergic toxidrome") cause different signs and symptoms, depending on whether the nicotinic or muscarinic receptors are involved? (Choose **ALL** correct answers.)

    A. Because some nicotinic and muscarinic receptors are located in and affect different anatomic structures.
    B. Because nicotinic and muscarinic receptors are triggered by different neurotransmitters.
    C. Because nicotinic and muscarinic receptors have different mechanisms of action.
    D. None of the above.

    To review relevant content, see "Types of Cholinergic Receptors" in this section.

Section 2: Nicotinic Acetylcholine Receptors

Learning Objectives	Upon completion of this section, you will be able to: • Describe the key function of nicotinic receptors. • Describe where nicotinic receptors are found. • Identify the key physiological effects that result from stimulation of nicotinic receptors by excessive amounts of acetylcholine.
Key Function of Nicotinic Receptors	The key function of nicotinic receptor proteins is to ***trigger*** **rapid neural and neuromuscular transmissions.** For those interested in learning about the molecular physiology of nicotinic receptors, the subject is discussed as optional reading below.
Molecular Physiology of Nicotinic receptors (Chemical-Gated Na^+ Channels) ***(Optional Reading)***	***Physiology of Nicotinic Receptors*** The nicotinic receptors are cylindrically-shaped proteins imbedded in synaptic walls that act as chemically-controlled sodium channels (also called *ligand-gated* sodium channels) that penetrate through the cell walls of post-synaptic nerves and myocytes at the *skeletal* neuromuscular junctions. (Guyton and Hall 2006) (See **Figure 6** below) (*Smooth muscle* contraction is controlled by muscarinic receptors, which are different and will be discussed later.) When the neurotransmitter, acetylcholine, attaches to the portion of the nicotinic receptor outside of the cell wall, it induces a conformational change that selectively opens up the channel to sodium ions. The resulting influx of positively charged sodium then triggers membrane depolarization. Depolarization is followed by the opening of other transmembrane channels that selectively allow the flow of K^+ ions into the cell. This results in repolarization. The period between depolarization and repolarization is called the **refractory period**. This is because during this time the cell cannot be depolarized by an additional stimulus. (Guyton and Hall 2006) The channel opening in the nicotinic receptor normally lasts less than a millisecond because the enzyme, cholinesterase, rapidly breaks down acetylcholine. Since channel opening is triggered by the attachment of a chemical (or "ligand") --- in this case, acetylcholine --- these channels are called **chemical- or ligand-gated channels**. As long as the chemical (in this case acetylcholine) is attached, the channel stays open. (Guyton and Hall 2006) Toxic levels of cholinesterase inhibitors prevent the breakdown of acetylcholine. As a result, the chemical-gated nicotinic receptor Na^+ channels are held in the open position, and a constant state of depolarization occurs. This results in a prolonged refractory period, during which no further transmission can occur. This is referred to as a **depolarization block**, and is similar to the depolarization block caused by succinylcholine. (Taylor 2001)

	Clinical Picture Due to Nicotinic Effects of Cholinesterase Inhibitors These events help to explain why the initial phase of toxicity is manifested by over-stimulation (characterized by myoclonic jerks, fasciculations and muscle spasms) followed by weakness progressing to paralysis.
Molecular Structure and Physiology of the Nicotinic Receptor ***(Optional Reading)***	 **Figure 6.** The nicotinic receptor. Figure modified with permission from: Guyton AC, Hall JE: Textbook of Medical Physiology (2006) Elsevier Saunders, Philadelphia. P.87. Used with permission.
Locations of Nicotinic Receptors	Nicotinic receptors are located in the (See also **Figure 6**) • Skeletal neuromuscular junctions. • Sympathetic and parasympathetic nervous system. • Autonomic ganglia. • Central nervous system.

Clinical Findings Due to Nicotinic Stimulation from Cholinesterase Inhibitors	Clinical findings are related to effects on the:
	
	• Neuromuscular junctions of skeletal muscles.
	  o Fasciculations and myotonic jerks, followed by weakness and paralysis.
	• Sympathetic nervous system (due to ganglionic stimulation of the adrenal gland). (See **Figure 5**)
	  o Hyperglycemia, glycosuria, ketosis. (Schenker, Louie *et al.* 1998; Clark 2002)
	  o Hypertension. (Erdman 2004)
	  o Leukocytosis with a left shift. (Schenker, Louie *et al.* 1998; Tareg *et al.* 2001)
	  o Mydriasis (pupillary dilation) (Erdman 2004) (in up to 13% of the cases (Clark 2002)).
	  o Sweating.
	  o Tachycardia, tachydysrhythmias. (Erdman 2004)
	  o Urinary retention. (Clark 2002)

Nicotinic Mnemonic

The table below shows a mnemonic for remembering the nicotinic signs of cholinesterase inhibitor toxicity**.**

Monday	**M**ydriasis (pupillary dilation)
Tuesday	**T**achycardia
Wednesday	**W**eakness
T**h**ursday	**H**ypertension
Friday	**F**asciculations

Key Points

- A key function of nicotinic receptors is to trigger *rapid* neural and neuromuscular transmission.
- Nicotinic receptors are found in:
  - The somatic nervous system (neuromuscular junctions in skeletal muscles).
  - The sympathetic and parasympathetic nervous system (autonomic ganglia).
  - The central nervous system (Discussed later).
- Peripheral nervous system clinical findings include
  - Fasciculations and myotonic jerks (central nervous system effects are discussed later).
  - Weakness and paralysis.
  - Sweating.
  - Mydriasis (pupillary dilation) (in up to 13% of the cases).
  - Tachycardia, tachydysrhythmias.
  - Hypertension.
  - Hyperglycemia, glycosuria, ketosis.
  - Leukocytosis with a left shift.

Progress Check

12. Nicotinic receptors: (Choose **ALL** correct answers.)

    A. Trigger rapid neural transmission.
    B. Trigger rapid neuromuscular transmission.
    C. Become stimulated then paralyzed by toxic levels of acetylcholine.
    D. Are found only in the autonomic nervous system.
    E. None of the above.

    To review relevant content, see "Key Functions of Nicotinic Receptors" in this section.

13. Over stimulation of nicotinic receptors can cause: (Choose **ALL** correct answers.)

    A. Tachycardia.
    B. Fasciculations.
    C. Mydriasis (pupillary dilation).
    D. Leucopenia.
    E. None of the above.

    To review relevant content, see "Clinical Findings Due to Nicotinic Stimulation from Cholinesterase Inhibitors" in this section.

14. Nicotinic receptors are found in which of the following locations: (Choose **ONE** best answer.)

    A. Sympathetic nervous system.
    B. Parasympathetic nervous system.
    C. Central nervous system.
    D. All of the above.
    E. None of the above.

    To review relevant content, see "Nicotinic Mnemonic" in this section.

Section 3: Muscarinic Acetylcholine Receptors

Learning Objectives

Upon completion of this section, you will be able to:

- Describe the key ways that muscarinic receptors differ from nicotinic receptors.
- Describe where muscarinic receptors are found.
- Identify the key physiological effects that result from stimulation of muscarinic receptors by excessive amounts of acetylcholine.

Muscarinic, G-Protein Mediated Receptors

The key response differences between muscarinic and nicotinic receptors is that the response of muscarinic receptors: (Hoffman and Taylor 2001)

- Is slower.
- May be excitatory or inhibitory.
- Do not affect skeletal muscles, but do influence the activity of smooth muscle, exocrine glands, and the cardiac conduction system. In contrast to skeletal muscle and neurons, smooth muscle and the cardiac conduction system normally exhibit intrinsic electrical and mechanical rhythmic activity. This activity is **modulated, rather than initiated,** by the muscarinic receptors. (Hoffman and Taylor 2001) For those interested in how muscarinic receptors work at the molecular level, the subject is covered in the Optional Reading below.

Molecular Physiology of Muscarinic Receptors

(Optional Reading)

Muscarinic acetylcholine receptors --- like nicotinic receptors -- are proteins that extend through the cell membrane from the outside to the inside.

However, they do not contain channels to allow ions inside the cell. Instead, when acetylcholine attaches to the external part of the muscarinic receptor, the internal portion of the receptor releases large guanine nucleotide binding proteins (G-Proteins) (See note below), inside the cell. G-proteins then initiate other activities within the cell, such as smooth muscle contraction, gland excretion, etc. (Hoffman and Taylor 2001; Mailman and Lawler 2001; Guyton and Hall 2006)

Note on G-Proteins: Many functions of the nervous system (*e.g.,* memory) require prolonged changes in neurons after the initial neurotransmitter is gone. Ligand-gated channels (such as those found in nicotinic receptors) are not suitable for this because the channels close in milliseconds. Prolonged changes can be achieved, however by activating G-proteins inside the post-synaptic neuron. It is then the G-proteins that trigger the prolonged effects. (Guyton and Hall 2006)

Molecular Structure and Physiology of Muscarinic Receptors

(Optional Reading)

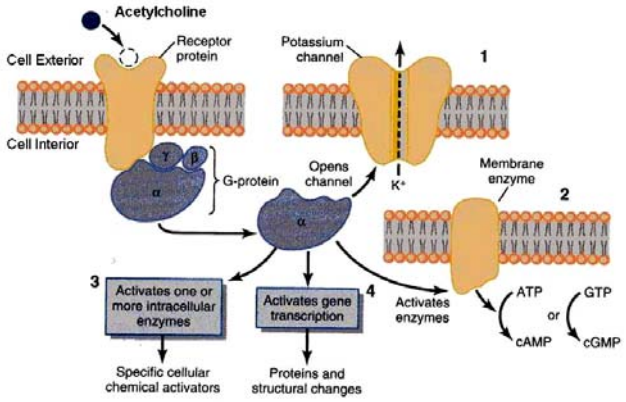


Figure 7. The muscarinic (G-protein) receptor. Modified with permission from: Guyton AC, Hall JE: Textbook of Medical Physiology (2006) Elsevier Saunders, Philadelphia. p. 561. Used with permission.

Where Muscarinic Receptors Are Located

Muscarinic receptors are located in the: (See also **Figure 5**)

- **Parasympathetic** nervous system.
  - Cardiac conduction system.
  - Exocrine glands.
  - Smooth muscles.
- **Sympathetic** nervous system.
  - Sweat glands.
- **Central** nervous system.

Clinical Effects on the Peripheral Nervous System Due to Excessive Stimulation of Muscarinic Receptors

Excessive Stimulation of muscarinic receptors due to cholinesterase inhibitor poisoning results in increased **parasympathetic:** (Erdman 2004)

- Cardiac effects.
  - AV blocks, with escape rhythms.
  - Bradycardia.
  - Ventricular dysrhythmias.
- Exocrine gland activity.
  - Bronchorrhea.
  - Hyperamylasemia.
  - Lacrimation.
  - Rhinorrhea.
  - Salivation.

- Smooth muscle activity.
  - Bladder stimulation, sphincter relaxation.
  - Bronchospasm.
  - Miosis (pupillary constriction), eye pain due to ciliary spasm.
  - Nausea, vomiting, cramps, diarrhea.

Peripheral Muscarinic Effects

The table below summarizes the peripheral mostly **parasympathetic*** (**muscarinic**) effects of cholinesterase inhibitors. (Ecobichon 1996; Sidell 1997; Reigart and Roberts 1999; Tareg *et al.* 2001) (See also **Figure 5**)

* Sweat glands, which are enervated by the **sympathetic nervous system**, are activated via muscarinic receptors.

End Organ Effected	Parasympathetic (Muscarinic) Effects
Respiratory tract	• Bronchorrhea (thick, mucoid secretions). • Bronchospasm. • Chest tightness. • Dyspnea. • Productive cough. • Rhinorrhea.
Eyes	• Blurred vision (especially, difficulty focusing on near objects). • Conjunctival injection. • Dimness of vision. • Miosis (pupillary constriction).
Gastrointestinal tract	• Cramping. • Diarrhea. • Incontinence. • Nausea. • Vomiting
Urinary tract	• Incontinence. • Urination.
Cardiovascular system	• AV block. • Bradycardia. • Hypotension. • Idioventricular rhythm. • Ventricular dysrhythmias (Torsades des points).
Exocrine glands	• Hyperamylasemia. • Lacrimation. • Salivation.
Note: Reflex nausea and vomiting may occur with isolated eye exposure, even in the absence of systemic toxicity. (Sidell 1997)	

Muscarinic Mnemonics

Two mnemonics are helpful to remember the **muscarinic** (mostly parasympathetic*) peripheral effects of cholinesterase inhibitors. (Clark 2002; Robey and Meggs 2004)

***Sweating/diaphoresis is a muscarinic effect, but is actually mediated via the *sympathetic* nervous system.

SLUDGE	**DUMBELS**
Salivation	**D**efecation/**D**iaphoresis
Lacrimation	**U**rination
Urination	**M**iosis (pupillary constriction)
Defecation	**B**ronchospasm and Bronchorrhea
GI pain	**E**mesis
Emesis	**L**acrimation
	Salivation

Key Points

- Muscarinic receptors respond more slowly than nicotinic receptors.
- The effects of muscarinic receptors may be excitatory or inhibitory.
- Muscarinic receptors do not affect skeletal muscles, but do influence the exocrine glands as well as the inherent activity of smooth muscles and the cardiac conduction system.
- In contrast to skeletal muscle and neurons, smooth muscle and the cardiac conduction system normally exhibit intrinsic electrical and mechanical rhythmic activity. This activity is **modulated, rather than initiated,** by the muscarinic receptors.
- With the exception of the sweat glands (enervated by the sympathetic nervous system), the peripheral nervous system effects (on the cardiac conduction system, exocrine glands, and smooth muscle) mediated by muscarinic receptors are parasympathetic.

Progress Check

15. When compared with the action of nicotinic receptors, muscarinic receptors: (Choose **ALL** correct answers.)

    A. Are faster.
    B. Initiate rather than modulate smooth muscle activity.
    C. Have primarily parasympathetic effects on the peripheral nervous system.
    D. Stimulate sweating via the sympathetic nervous system.
    E. None of the above.

    To review relevant content, see "Muscarinic G-Protein Mediated Receptors" in this section.

16. Cholinesterase inhibitor toxicity leads to the following clinical findings mediated by muscarinic receptors: (Choose **ALL** correct answers.)

    A. Miosis (pupillary constriction).
    B. Bronchorrhea.
    C. Nausea.
    D. Bronchospasm.
    E. None of the above.

    To review relevant content, see "Muscarinic Mnemonic" in this section.

17. Muscarinic receptors are found in: (Choose **ALL** correct answers.)

    A. Skeletal muscle.
    B. Smooth muscle.
    C. Exocrine glands.
    D. Sweat glands.
    E. None of the above.

    To review relevant content, see "Where Muscarinic Receptors Are Located" in this section.

Section 4: Clinical Findings in Cholinesterase Inhibitor Toxicity Are Due to a Mixture of Nicotinic and Muscarinic Effects

Learning Objectives

At the completion of this section, the reader will be able to describe:

- The factors that account for variation in the clinical presentation of cholinesterase toxicity.
- The CNS effects of cholinesterase inhibitor toxicity.
- What is known about the nicotinic and muscarinic effects of cholinesterase toxicity on the central nervous system?
- Four factors contributing to respiratory failure and death in cases of cholinesterase inhibitor toxicity.

Sympathetic vs. Para-Sympathetic Effects

Nicotinic and muscarinic receptor stimulation results in a mixture of their sympathetic and parasympathetic effects. (Erdman 2004)

Cholinergic stimulation of the **nicotinic** receptors in the **sympathetic** autonomic ganglia may cause adrenal medullary catecholamine release leading to increased heart rate, and blood pressure, and (in about 13% of the time) mydriasis (pupillary dilation). (Erdman 2004)

More often, however, autonomic findings of **parasympathetic** stimulation predominate over **sympathetic** findings. (Erdman 2004)

NOTE: For reasons which are presently unclear, **nicotinic** signs predominate in **pediatric** cholinesterase inhibitor poisoning. (More on this later.)

The differences in nicotinic and muscarinic structure and function explain why cholinesterase inhibitor toxicity results in **muscarinic** stimulation of the cardiac conduction system, smooth muscle, and exocrine glands but **nicotinic** stimulation, ***then subsequent weakness and paralysis*** of skeletal muscles.

Central Nervous System (CNS) Effects	The pathophysiology of cholinesterase inhibitors on the CNS is complex and poorly understood. Both Nicotinic and muscarinic receptors are involved. (Erdman 2004) CNS findings that have been reported include

Anxiety (Carlton, Simpson *et al.* 1998)	**Arreflexia** (Carlton, Simpson *et al.* 1998)	**Circulatory depression** (Carlton, Simpson *et al.* 1998)
Coma (Clark 2002)	**Confusion** (Ecobichon 1996; Clark 2002)	**Convulsions**
Depression (Reigart and Roberts 1999)	**Drowsiness** (Ecobichon 1996)	**Emotional lability** (Sidell 1997; Romano, McDonough *et al.* 2001)
Excess dreaming (Romano, McDonough *et al.* 2001)	**Fatigability** (Sidell 1997)	**Hallucinations** (Clark 2002)
Headache (Ecobichon 1996)	**Insomnia** (Sidell 1997; Carlton, Simpson *et al.* 1998)	**Lethargy** (Ecobichon 1996)
Memory loss (Reigart and Roberts 1999)	**Nightmares** (Sidell 1997)	**Restlessness** (Carlton, Simpson *et al.* 1998)
Respiratory-depression (Carlton, Simpson *et al.* 1998)	**Tension** (Sidell 1997)	**Tremulousness, jitteriness** (Sidell 1997)
Note: Psychological and behavioral effects have been noted to precede physical symptoms. (Romano, McDonough *et al.* 2001) [Although rapid onset of severe poisoning may obscure this.]		

Cause of Death	Death is usually due to respiratory failure from: (Zwiener and Ginsburg 1988; Sofer, Tal *et al.* 1989; Reigart and Roberts 1999) • Bronchoconstriction. • Bronchorrhea. • Central respiratory depression. • Weakness and paralysis of respiratory muscles.
Frequency of Signs and Symptoms	The likelihood of signs and symptoms of cholinesterase toxicity in a given individual depends on the specific chemical, the dose, and the route of exposure. (See more about this in the Optional Reading in the following section.) These may range from a mild, flu-like syndrome to rapid collapse, paralysis, respiratory arrest, and death. (Carlton *et al.* 1998) **Figure 8** in the following Optional Reading shows the frequency of signs and symptoms from eight case series of cholinesterase inhibitor poisoning. (Tsachalinas, Logaras *et al.* 1971; Hayes, van der Westhuizen *et al.* 1978; Hirshberg and Lerman 1984; Midtling, Barnett *et al.* 1985; Goswamy, Chaudhuri *et al.* 1994; Nouira, Abroug *et al.* 1994; Singh, Batra *et al.* 1995; Okumura, Takasu *et al.* 1996)

MISCONCEPTION: As noted in the mnemonics, SLUDGE AND DUMBELS, diarrhea, urinary incontinence, and excessive lacrimation are common signs of cholinesterase inhibitor poisoning.

REALITY: Although nausea and vomiting are common with moderate exposures, diarrhea (listed as "defecation" in the above mnemonics), and urination are infrequent. (Leikin, Thomas *et al.* 2002) As noted in the table above, Lacrimation is also not a common finding.

Frequency of Signs and Symptoms in Cholinesterase Inhibitor Toxicity *(Optional Reading)*

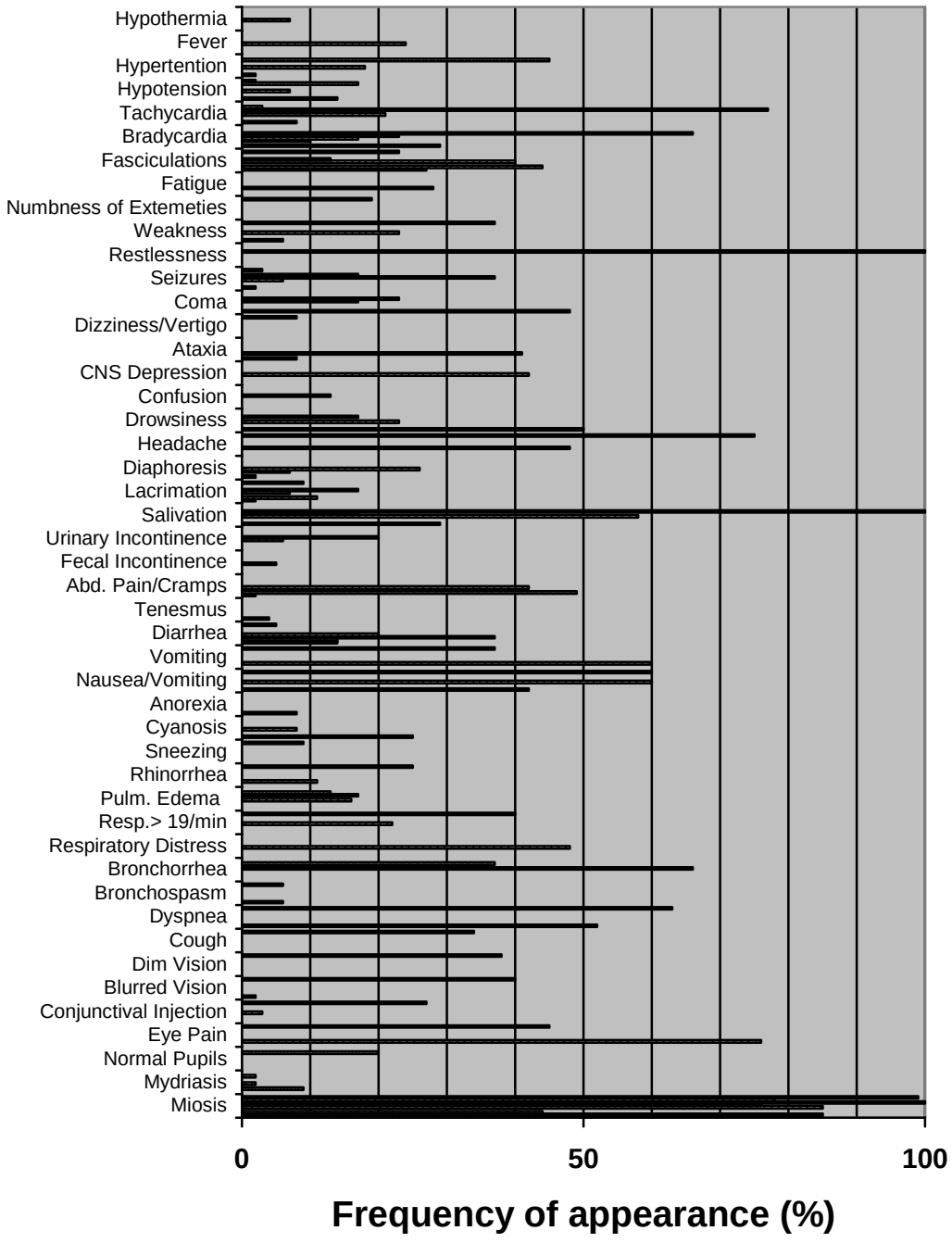


Figure 8. Frequency of Signs and Symptoms in Cholinesterase Inhibitor Toxicity.

Key Points

- Signs and symptoms of cholinesterase inhibitor poisoning may vary among individuals, depending on the:
  - Age of the patient.
  - Dose.
  - Route of exposure.
  - Specific cholinesterase inhibitor involved.
- Central nervous system effects are due to the presence of both nicotinic and muscarinic receptors.
- Central nervous system signs and symptoms are non-specific and can suggest mental illness.
- Death is usually due to respiratory failure caused by
  - Bronchoconstriction.
  - Bronchorrhea.
  - Central respiratory depression.
  - Weakness and paralysis of respiratory muscles.

Progress Check

18. Signs and symptoms of cholinesterase inhibitor poisoning: (Choose **ALL** correct answers.)

    A. May vary depending on the specific chemical involved.
    B. Are dominated by nicotinic findings in pediatric cases.
    C. Involving the CNS are primarily due to the presence of muscarinic receptors.
    D. May mimic mental illness.
    E. None of the above.

    To review relevant content, see "Sympathetic vs. Parasympathetic Effects" in this section.

19. Death from cholinesterase inhibitor poisoning is usually due to: (Choose the **ONE BEST** answer.)

    A. Cardiac failure.
    B. Respiratory failure.
    C. Renal failure.
    D. Hepatic failure.
    E. None of the above.

    To review relevant content, see "Cause of Death" in this section.

20. Which of the following are true about the central nervous system effects of cholinesterase inhibitors? (Choose the **ONE BEST** answer.)

    A. The pathology can be explained on the basis of increased muscarinic, as opposed to nicotinic, receptor activity.
    B. The pathology can be explained on the basis of increased nicotinic, as opposed to muscarinic, receptor activity.
    C. The pathology is poorly understood but involves both nicotinic and muscarinic receptors.
    D. None of the above.

    To review relevant content, see "Central Nervous System (CNS) Effects" in this section.

21. Which of the following central nervous system signs and symptoms have been reported in cases of cholinesterase inhibitor poisoning? (Choose **ALL** correct answers.)

    A. Anxiety.
    B. Emotional lability.
    C. Convulsions.
    D. Excess dreaming.
    E. None of the above.

    To review relevant content, see "Central Nervous System (CNS) Effects" in this section.

Section 5: Signs and Symptoms by Route of Exposure and Chemical Structure of the Involved Cholinesterase Inhibitor *(Optional Reading)*

Learning Objectives *(Optional Reading)*

Upon completion of this portion of the case study, the learner should be able to describe how:

- Signs and symptoms of cholinesterase toxicity vary with the route of exposure.
- Cholinesterase toxicity relates to the chemical structure of the cholinesterase inhibitors.

Signs and Symptoms by Route of Exposure *(Optional Reading)*

Cholinesterase inhibitors may be rapidly absorbed via dermal, conjunctival, respiratory, and gastrointestinal routes. (Carlton, Simpson *et al.* 1998) Other factors being equal (*e.g.,* chemical structure), signs and symptoms may vary by route of exposure (although any constellation of findings can occur with significant exposure by any route). (Sidell 1997; Carlton, Simpson *et al.* 1998; Leikin, Thomas *et al.* 2002; Erdman 2004)

Exposure Route	Rapidity of Onset of Clinical Findings
Inhalation	The most rapid (seconds to minutes).
Ingestion	Intermediate (typically within 30-90 minutes).
Dermal	The slowest (may be up to 18 hours).

Note: *Very high doses* of nerve agents can act within minutes, even with dermal exposures. (Sidell 1997)

Chemical Structure *versus* Toxicity *(Optional Reading)*

Among other factors, the toxicity of cholinesterase inhibitors varies with chemical structure.

For example: (Besser and Gutmann 1994)

- Organophosphorus compounds having a quaternary nitrogen (ammonium) attached to the phosphorus atom have the highest toxicity.
- Also very toxic are those containing an attached fluorine atom (This includes the chemical warfare nerve agents).
- Less toxic are those containing a cyanide or halogen other than fluorine.
- Less toxic still are those with attached alkyl, alkoxy, alkylthio, aryloxy, arylthio, heterocyclic analogs, or nonquaternary nitrogen. Most organophosphorus compounds belong to this category.

Vapor Exposure (Namba, Nolte *et al.* 1971; Tareg *et al.* 2001) **(Conjunctival and Respiratory)** ***(Optional Reading)***	**Note:** Mild vapor exposure may produce eye and respiratory symptoms due to localized tissue contact even in the absence of other systemic findings.

Mild	• Bronchoconstriction, chest tightness. • Dim or blurred vision, conjunctival injection. • Mild increase in bronchial secretions. • Miosis (pupillary constriction) with eye pain or headache. • Rhinorrhea.
Moderate	• Coughing, wheezing. • Fasciculations, generalized weakness. • Nausea, vomiting. • Shortness of breath, dyspnea.
Severe	• Coma, seizures. • Flaccid paralysis, apnea. • Severe bronchorrhea and bronchospasm. • Death (within minutes with nerve agents).

Dermal Exposure (Sidell 1997; Tareg *et al.* 2001) ***(Optional Reading)***	**Notes:** With dermal exposure to nerve agents onset of clinical findings of the cholinergic toxidrome may be delayed up to 18 hours. (Sidell 1997) Thus, patients with suspected dermal exposure should be observed and monitored. No definite minimum, safe duration of observation has yet been established because of lack of clinical experience and clinical studies. (Leikin, Thomas *et al.* 2002) Respiratory symptoms may be absent in mild to moderate exposures. (Leikin, Thomas *et al.* 2002) A substantial proportion of those with isolated dermal exposure do not develop miosis (pupillary constriction). (Sidell 1997)

Mild	• Fasciculations at site of exposure. • Increased sweating at site of exposure.
Moderate	• Diarrhea. • Generalized weakness.

	• Nausea. • Vomiting.
Severe	• Apnea. • Coma. • Convulsions (secondary urinary/fecal incontinence). • Flaccid paralysis. • Generalized fasciculations. • Generalized secretions.

Oral Exposure ***(Optional Reading)***	The frequency and sequence of clinical findings after ingesting cholinesterase inhibitors have received less attention in the literature. Generally, with this route, gastrointestinal signs and symptoms are the first to appear. (Carlton, Simpson *et al.* 1998; Tareg *et al.* 2001; Erdman 2004) • Abdominal cramps. • Anorexia. • Diarrhea. • Nausea. • Vomiting. **Note:** Cholinesterase inhibiting insecticides are often dissolved in hydrocarbons, and ingestion may be associated with pulmonary aspiration and chemical pneumonitis, as well as a solvent-like breath odor. (Durham and Hayes 1962; Clark 2002)
Reasons for Delayed Onset of Clinical Findings ***(Optional Reading)***	Delayed onset may occur with: • Dermal exposure. • Cholinesterase inhibitors which can be stored in fat tissue and released over time (*e.g.,* dichlofenthion). (Clark 2002) • Cholinesterase inhibitors whose toxicity requires metabolic conversion (*e.g.,* malathion). **Note**: In some cases, deceptively mild initial symptoms may be followed by a rapid worsening up to 48 hours later. This may occur even while the patient is undergoing antidotal treatment. (Erdman 2004)
Key Points ***(Optional Reading)***	• Cholinesterase inhibitors may be rapidly absorbed via dermal, conjunctival, respiratory, and gastrointestinal routes.

Section 6: Effects on Routine Laboratory Tests

Learning Objectives

Upon completion of this section, you should be able to

- Describe what routine laboratory tests can be altered by acute cholinesterase inhibitor toxicity.

Introduction

Routine laboratory test results are usually normal in patients with cholinesterase inhibitor toxicity. However, a few notable exceptions may confound the diagnosis. Examples are listed in the table below. (Schenker, Louie *et al.* 1998; Tareg *et al.* 2001; Wiener and Hoffman 2004)

Laboratory Test	Results that May Occur in Cholinesterase Inhibitor Toxicity	Presumed Cause
EKG **Note**: In a series of 105 cases, Hayes *et al.* found that --- with the exception of rate changes --- EKG abnormalities occurred only 5% of the time. (Hayes, van der Westhuizen *et al.* 1978)	• Tachycardia or bradycardia (Leikin, Thomas *et al.* 2002) • A-V block (Suzuki, Kohno *et al.* 1997) Prolonged Q-T (Clark 2002) • Peaked T-waves (Hayes, van der Westhuizen *et al.* 1978) • Torsades de pointes (Leikin, Thomas *et al.* 2002)	
Ketoacidosis	Present (Schenker, Louie *et al.* 1998)	n/a
Serum amylase	Elevated (Tareg *et al.* 2001; Wiener and Hoffman 2004)	Injury to pancreas from parasympathetic over-stimulation and hypersecretion (Tareg *et al.* 2001)
Serum creatine kinase (CK)	Elevated (Okumura, Takasu *et al.* 1996; Wiener and Hoffman 2004)	Fasciculations, seizures
Serum glucose	Elevated (Hayes, Wise *et al.* 1980; Schenker, Louie *et al.* 1998; Tareg *et al.* 2001)	Nicotinic effect on the adrenal medulla with catecholamine release (Tareg *et al.* 2001)
Serum lipids and triglycerides	Decreased (Wiener and Hoffman 2004)	n/a

Serum potassium	Decreased (Suzuki, Kohno *et al.* 1997; Tareg *et al.* 2001; Wiener and Hoffman 2004) Increased	Nicotinic effect on the adrenal medulla with catecholamine release (Tareg *et al.* 2001) Effect of muscular activity during seizures
Urine glucose	Elevated (Hayes, Wise *et al.* 1980; Schenker, Louie *et al.* 1998; Tareg *et al.* 2001)	Nicotinic effect on the adrenal medulla with catecholamine release (Tareg *et al.* 2001)
Urine proteins	Elevated (Hayes, Wise *et al.* 1980; Schenker, Louie *et al.* 1998; Tareg *et al.* 2001)	n/a (Tareg *et al.* 2001)
White blood cell count	Elevated with a left shift (Hayes, Wise *et al.* 1980; Okumura, Takasu *et al.* 1996; Schenker, Louie *et al.* 1998; Tareg *et al.* 2001)	Nicotinic effect on the adrenal medulla with catecholamine release (Tareg *et al.* 2001)
n/a = not addressed in the reference.		

Key Points

- A number of routine laboratory tests can be altered due to the cholinergic toxidrome of cholinesterase toxicity.
- These can lead to misdiagnosis.

Progress Check

22. Cholinesterase toxicity has been known to cause abnormally high levels of which of the following laboratory tests. (Choose **ALL** correct answers.)

    A. Serum glucose.
    B. White blood cell count.
    C. Serum amylase.
    D. CPK.
    E. None of the above.

    To review relevant content, see "Introduction" in this section.

Section 7: Differential Diagnosis of the Cholinergic Toxidrome

Learning Objectives

Upon completion of this section, you should be able to

- Identify other medical conditions that could be mimicked by the cholinergic toxidrome.

Conditions that Can be Mimicked by Cholinesterase Inhibitor Toxicity

In some cases, diagnosis may be difficult, particularly in pediatric cases (Sofer, Tal *et al.* 1989; Tareg *et al.* 2001; Erdman 2004) (discussed more later) and the early stages of toxicity when symptoms may be mild and non-specific. (Erdman 2004) In one study, 16 of 20 transferred patients with cholinesterase inhibitor toxicity were misdiagnosed. (Carlton, Simpson *et al.* 1998)

One report on organophosphate poisoning suggested that the most common mistake was to misdiagnose cases presenting with vomiting, diarrhea, and abdominal pain as gastroenteritis. (Hayes, van der Westhuizen *et al.* 1978)

Some examples of conditions that could be mimicked by cholinesterase inhibitor poisoning are shown in the table below.

Cholinesterase Inhibitor Clinical Finding(s)	Condition(s) Mimicked
• Chest discomfort • Rhinorrhea	Viral respiratory infection (common “cold”) (Gaon and Werne 1955)
• Cough • Fatigue • Fever • Headache • Nausea • Rhinorrhea • Vomiting	Influenza (Carlton, Simpson *et al.* 1998)
• Anxiety, • Confusion • Depression • Emotional lability • Fatigue • Hallucinations • Headache • Insomnia • Toxic psychosis	Mental illness (Gershon and Shaw 1961)

• Coma • Confusion • Hyperglycemia • Ketosis • Tachypnea	Diabetic ketoacidosis (Clark 2002)
• Diarrhea • Fever • Nausea • Vomiting	Gastroenteritis, food poisoning (Tareg *et al.* 2001)
• Altered mental status • Fever • Leukocytosis • Weakness	Pneumonia (Perrone, Henretig *et al.* 2003), meningitis
• Muscle weakness	Myasthenia crisis, (Erdman 2004) Guillain-Barré syndrome (Tareg *et al.* 2001)
• Nicotinic signs and symptoms	Nicotine poisoning (Erdman 2004)
• Muscarinic signs and symptoms	Cholinergic drug (*e.g.,* pilocarpine, carbachol, bethanechol, or methacholine) overdose (Erdman 2004)
• Altered mental status • Miosis (pupillary constriction)	Opiate overdose, pontine infarction (Tareg *et al.* 2001)
• Altered mental status • Ataxia	Intoxication, (Reigart and Roberts 1999) brain injury (Wyckoff, Davies *et al.* 1968)
• Altered mental status • Hypertension	Hypertensive encephalopathy (Wyckoff, Davies *et al.* 1968)
• Bronchorrhea • Dyspnea, • Tachypnea • Wheezing	Asthma attack (Tareg *et al.* 2001)
• Altered mental status • Dyspnea • Fever • Solvent breath odor • Tachypnea	Hydrocarbon ingestion with aspiration pneumonia (Clark 2002)

• Cardiac dysrhythmias • Chest tightness • Dyspnea • Diaphoresis • Dizziness • Nausea • Peaked T waves (Hayes, van der Westhuizen *et al.* 1978) • Râles • Vomiting	Coronary ischemia, myocardial infarction, congestive heart failure, or cardiogenic shock
• Altered mental status • Coma • Fasciculations • History of pesticide exposure • Nausea, • Respiratory difficulty • Salivation • Seizures • Vomiting	Severe pyrethroid insecticide* toxicity (Holland 2002)
* Misdiagnosing this for cholinesterase inhibitor poisoning could lead one to mistakenly administer toxic doses of atropine. (The treatment of pyrethroid poisoning is benzodiazepines or Phenobarbital for seizures, together with supportive care.) (Holland 2002)	

Differential Diagnosis

Several findings can help differentiate cholinesterase inhibitor toxicity from other conditions:

- A history of exposure, especially with multiple victims and similar clinical findings. (See Exposure History, Section 9)
- Response to an atropine challenge. The failure to show signs of atropinization after a trial dose of atropine is said to suggest cholinesterase poisoning. This topic is discussed in detail in the Section 11, Management Strategy 3: Medications.
- The presence of fasciculations and weakness (These signs are considered by some to be the most reliable findings in cholinesterase toxicity). (Clark 2002) Although miosis (pupillary constriction) can be absent or can reflect other conditions, its presence still should raise a high level of suspicion.

Key Points

- The cholinergic toxidrome can be misdiagnosed because its signs and symptoms mimic a number of other illnesses.
- The factors most useful in differential diagnosis are:
  - A history of exposure to cholinesterase inhibitors.
  - The presentation of multiple victims with similar findings.
  - The presence of fasciculations and muscle weakness.
  - Response to an atropine challenge.
  - Miosis (pupillary constriction) is a helpful sign, even though mydriasis (pupillary dilation) has been reported instead in up to 13% of the cases.

Progress Check

23. Cholinesterase inhibitor toxicity can be mistaken for a number of other illnesses. Which of the following indicate that the condition is not due to cholinesterase toxicity? (Choose **ALL** correct answers.)

    A. Presence of fever.
    B. Lack of urinary incontinence.
    C. solvent-like breath odor.
    D. leukocytosis with a left shift.
    E. none of the above.

    To review relevant content, see "Conditions that Can be Mimicked by Cholinesterase Inhibitor Toxicity" in this section.

Section 8: Signs and Symptoms: Differences in Pediatric Cases

Learning Objectives

Upon completion of this section, you should be able to

- Identify how the clinical presentation in pediatric cases of the cholinergic toxidrome differs from that in adults.

Differences in Pediatric Cases

Pediatric cases may present with clinical findings that are different than in adults. Examples include:

- Bradycardia, fasciculations, lacrimation, and sweating are less common. (Sofer, Tal *et al.* 1989)
- Common presenting signs are lethargy, coma, seizures, flaccid muscle weakness, miosis (pupillary constriction), tachycardia, and excessive salivation. (Sofer, Tal *et al.* 1989; Tareg *et al.* 2001)
- The predominant effects may be nicotinic instead of muscarinic, manifesting mainly as neuromuscular weakness (Tareg *et al.* 2001) and CNS effects. (Erdman 2004)
- While generalized seizures are not typical in adults except in severe nerve agent poisoning or massive doses of other organophosphorus compounds, they are common in pediatric patients. (Tareg *et al.* 2001)

Note: Neuromuscular weakness is easy to overlook in a small child --- who may appear very quiet and still --- unless muscle tone is specifically assessed. (Tareg *et al.* 2001)

Pediatric Signs and Symptoms

The frequency of pediatric signs and symptoms in cholinesterase poisoning is shown in the **Figure 9** below. (Sofer, Tal *et al.* 1989)

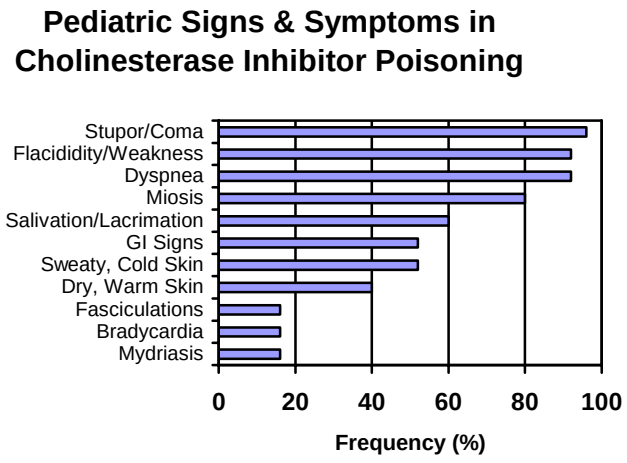


Figure 9. Pediatric signs and symptoms. Data from: Sofer S, Tal A, Shahak E. Carbamate and organophosphate poisoning in early childhood. Pediatric Emergency Care. 1989; 5:222-225.

Key Points

- Pediatric presentation of the cholinergic toxidrome from cholinesterase inhibitor toxicity tends to be different than in adults.

Progress Check

24. The cholinergic toxidrome in children is dominated by which type of signs and symptoms? (Choose the **ONE BEST** answer.)

    A. Muscarinic
    B. Nicotinic
    C. A and B.
    D. None of the above.

    To review relevant content, see "Differences in Pediatric Cases" in this section.

25. In the cholinergic toxidrome from cholinesterase inhibitors, seizures are (Choose **ALL** correct answers.)

    A. More common in adults.
    B. More common in children.
    C. About equally common in children and adults.
    D. Very rare in both adults and children.
    E. None of the above.

    To review relevant content, see "Differences in Pediatric Cases" in this section.

26. True or False: Neuromuscular weakness in a small child is easy to overlook unless muscle tone is specifically assessed.

    A. True.
    B. False.

    To review relevant content, see "Differences in Pediatric Cases" in this section.

Section 9: Importance of the Exposure History

Learning Objectives

Upon completion of this section, you should be able to

- Identify potential sources of exposure to cholinesterase inhibitors.
- Identify the important elements to include in an exposure history when evaluating patients who might be suffering from cholinesterase inhibitor toxicity.

Introduction

There does not appear to be much data on how often cholinesterase-based pharmaceuticals, plant and animal toxins, and industrial substances cause toxicity.

However, probably the most frequent source of cholinesterase inhibitor exposure is from pesticides. While estimates vary widely, one source suggests that pesticides cause 3 million poisonings and 200,000 deaths world-wide each year. The American Association of Poison Control Centers reported 86,914 pesticide exposures in 1996. (Clark 2002)

The exposure history can be a valuable aid in identifying patients who might be suffering from cholinesterase toxicity.

See the Case Study on Taking an Exposure History available at

http://www.atsdr.cdc.gov/csem/exphistory/

Note: While cholinesterase inhibitor poisoning may go unrecognized because of the failure to take an exposure history, the exposure history can also be deceiving. For example, In one study, 88% of parents of patients with organophosphate poisoning denied any exposure history. (Reigart and Roberts 1999)

Where Cholinesterase Inhibitors are Found

Some sources of cholinesterase inhibitors are listed in the following table.

Source	Examples
Pesticides	Carbamates Organophosphorus compounds
Nerve agents used in chemical warfare and chemical terrorism	Sarin Soman Tabun VX
Pharmaceuticals (Lotti 1992; Hoffman and Taylor 2001;	Donepezil used for Parkinsonism Neostigmine used for paralytic ileus or urinary bladder atony Physostigmine used for glaucoma or as an antidote for anticholinergic

Taylor 2001)	poisoning Pyridostigmine used for myesthenia gravis or prophylaxis against nerve agent exposure Tacrine used for Parkinsonism
Poisonous plants and animals (Karalliedde 1999; Kassa 2002)	Bittersweet Calabar beans Fish hunting cone snails Mushrooms Potato sprouts Venomous snakes
Industrial materials (Karalliedde 1999)	Fire retardants Lubricant additives Plasticizers
Traditional remedies (Karalliedde 2002)	Huperazine A (Chinese remedy) Solanine and chaconine in potatoes used in Africa to treat HIV

Home Exposures	Exposures occur in the home after it has been sprayed or fogged with pesticides. (Clark 2002) Outbreaks of poisoning have occurred from contaminated crops or food. (Erdman 2004) Suicidal ingestions are particularly widespread in countries, such as India, Sri Lanka, Turkey, Taiwan, and parts of Africa. (Ecobichon 1996). Children may be exposed when pesticides are stored in unlabeled containers or beverage bottles, or when they play in recently sprayed fields. Pesticides (including those that are cholinesterase inhibitors) were involved in 4.2% of poisonings in 2004 in children younger than 6 years of age. (Watson, Litovitz et al. 2004)

Occupational Exposures

Occupations associated with exposure to cholinesterase inhibitors include the following:

- Agricultural workers. (Ecobichon 1996; Jaga and Dharmani 2003)
- Crop duster pilots and ground crews. (Ecobichon 1996)
- Florists. (Jaga and Dharmani 2003)
- Gardeners and nursery workers. (Ecobichon 1996)
- Greenhouse workers. (Jaga and Dharmani 2003)
- Mosquito abatement workers. (Marrs and Dewhurst 2000)
- Pest control workers. (Ecobichon 1996)
- Pesticide applicators, exterminators. (Jaga and Dharmani 2003)
- Pesticide manufacturers. (Jaga and Dharmani 2003)
- Pet groomers.
- Veterinary workers. (Jaga and Dharmani 2003)

Consumer Exposures

Consumers can be exposed to cholinesterase inhibitors by means of the following:

- Spillage onto food products during storage or transport. (Marrs and Dewhurst 2000)
- Ingestion of seed grain or seed potatoes treated with pesticides (not intended for consumption). (Marrs and Dewhurst 2000)
- Improper application of pesticides.

Exposure History Questions

Below are some focused exposure history questions that should be asked of patients (and household members) when signs and symptoms are consistent with or suggestive of cholinesterase inhibitor toxicity.

- What kind of work do you do? (Inquire about work done by other residents of the household as well.)
- Describe typical work activities (tasks, locations, materials, and substances used).
- Describe any recent changes in work activities or changes that coincide with symptom development. Include any work done outside of regular employment (*e.g.,* volunteer work).
- What are your hobbies and outside activities (*e.g.,* gardening, flower arranging, animal-related activities)?
- Do you consume wild mushrooms?
- Do you handle venomous snakes?
- What chemicals are used at your work locations? Material Safety Data Sheets (MSDS), obtainable from employers, may contain valuable information about chemicals used at that location. While studies have shown that a significant number of MSDS documents contain incomplete or incorrect information, this mostly relates to chronic toxicity data.) (Greenberg, Cone et al. 1996)
- Are pesticides used or manufactured at your workplace?
- Do you transport chemicals? pesticides? (Specify product names.)
- Do you come into contact with them? When? How often? What type of contact? (Skin, inhalation?)
- Do symptoms occur at any particular time of day? day of week? after

any particular type of activity?

- Does anyone else at home or work have similar symptoms?
- What medicines have you been taking? Have you used any traditional or herbal remedies?
- Do you use pesticides at work?
- Do you use pesticides at home (*e.g.,* garden sprays or granules, flea or tick sprays or collars, animal shampoos)?
- When you use pesticides, do you wear protective gloves? respirator? clothing? Do you wash/shower/change clothes afterwards? Have you received instructions on the use of Personal Protective Equipment (PPE)? Does unwashed protective wear or work clothing come into contact with other household laundry?
- Do you shower/wash hands after using? Do you change clothes? Who handles the contaminated clothes? Do you smoke or eat prior to washing and changing clothes after handling pesticides?

Key Points

- Cholinesterase inhibitors are found in pharmaceuticals, pesticides, chemical warfare agents, industrial materials, and traditional medical remedies.
- Taking an exposure history may be helpful in diagnosing cholinesterase inhibitor toxicity

Progress Check

27. Potential sources of exposure to cholinesterase inhibitors include which of the following: (Choose **ALL** correct answers.)

    A. Pesticides.
    B. Pyridostigmine.
    C. Castor beans.
    D. Potato sprouts.
    E. None of the above.

    To review relevant content, see "Where Cholinesterase Inhibitors are Found" in this section.

28. Which of the following questions on an exposure history are appropriate for the physician to ask in a patient suffering from signs and symptoms suggestive of cholinesterase inhibitor poisoning?

    A. What are your hobbies?
    B. What kind of work do you do?
    C. Does anyone at home have similar signs or symptoms?
    D. Do you handle venomous snakes?
    E. None of the above.

    To review relevant content, see "Exposure History Questions" in this section.

Section 10: Laboratory Assessment of the Cholinergic Toxidrome

Red Blood Cell (RBC) and Serum Cholinesterase Levels

Learning Objective

Upon completion of this section, you will be able to:

- Describe the usefulness and limitations of laboratory analysis of RBC and serum cholinesterase levels.

MISCONCEPTION: Cholinesterase levels play an important role in the emergency diagnosis and treatment of cholinesterase inhibitor toxicity.

REALITY: Emergency assessment and treatment should be based on the patient's history, signs, and symptoms. (Wiener and Hoffman 2004) It should *not* be delayed to await the results of these laboratory tests, which are rarely available in time to guide emergency treatment! (Tareg *et al.* 2001)

Introduction

Circulating RBC and serum (uninhibited) cholinesterase levels are used to approximate levels in neural tissue, since the latter are impractical to obtain. (Clark 2002)

The Two Types of Cholinesterase Levels

There are two types of cholinesterase levels

- Red Blood Cell (RBC) cholinesterase (also called true cholinesterase).
- Serum cholinesterase (also called pseudocholinesterase or butyrylcholinesterase).

In general, the key differences between RBC cholinesterase and serum cholinesterase are shown in the following table.

	RBC cholinesterase	Serum cholinesterase
Accuracy*	Greater**	Less
Availability	Less	Greater
Duration of depression (Reigart and Roberts 1999)	Several days to a few weeks	1-3 months
Onset of depression	Later	Early

*That is, it is thought to more closely approximate cholinesterase levels in the neurosynapse.

**Although one author contends that there is no evidence that this is the case for nerve agents. (Wiener and Hoffman 2004)

Sources of Error in the Measurement of Cholinesterase Levels ***(Optional Reading)***	Listed below are some of the sources of error in the measurement and interpretation of cholinesterase levels. • Normal ranges of RBC and serum cholinesterase vary widely between individuals (and even in the same individual at different times). (Karalliedde 2002; Leikin, Thomas *et al.* 2002; Wessels, Barr *et al.* 2003; Wiener and Hoffman 2004) • Because of this, a person who usually has a "high-normal" level of cholinesterase could be significantly toxic but his or her cholinesterase level could decrease only into the "low-normal" range. (Tareg *et al.* 2001) • Thus, the toxic patient would have a falsely normal test result. (Midtling, Barnett *et al.* 1985; Jamal 1997; Clark 2002) (One author indicates that for serum cholinesterase there is a 300% difference between the lower and upper normal values. (Erdman 2004)) • Thus, unless pre-exposure levels are available for comparison, only a level of inhibition greater than that due to interindividual variability (about 25% for RBC cholinesterase) can be considered significant. (Ray 1998) • Errors in laboratory results can also occur if samples are stored at room temperature, because cholinesterase bound to un-aged inhibitors can undergo significant spontaneous reactivation. (Ray 1998) • Another source of error, even with modern testing kits, is lack of experience and skill of the laboratory technician. (Wessels, Barr *et al.* 2003)
Case Example ***(Optional Reading)***	In one study of 29 farm workers who were symptomatic after exposure to pesticides, none had RBC or serum cholinesterase levels below the lower limit of normal. (Midtling, Barnett *et al.* 1985)
Variations among Laboratories ***(Optional Reading)***	Due to differences in techniques, the absolute cholinesterase values vary from laboratory to laboratory. (Minton and Murray 1988) Laboratories may report their findings as percentages of average or normal (in unexposed subjects) rather than as absolute values.
Levels Correlated with Toxicity ***(Optional Reading)***	Even with the more accurate RBC cholinesterase, the point at which various authors have suggested that toxicity begins to appear ranges from 40% to 75% of normal values. (Carlton, Simpson *et al.* 1998) (Romano, McDonough *et al.* 2001; Clark 2002)
The Role of Baseline Cholinesterase Levels ***(Optional Reading)***	Some authors suggest that, when compared to an individual's baseline value, changes in RBC cholinesterase levels correlate well with cholinesterase inhibitor toxicity. (Tareg *et al.* 2001; Clark 2002) However, such baseline values are rarely available except, perhaps, in occupational settings where workers are monitored for ongoing exposures.

Other Causes of Cholinesterase Level Abnormalities	Other conditions, besides exposure to cholinesterase inhibitors can cause abnormalities in cholinesterase levels.

	RBC Cholinesterase	Serum Cholinesterase
Low levels	• Antimalarial drugs (Clark 2002) • Oral contraceptives (Clark 2002) • Some anemias (Tareg *et al.* 2001)	• Acute infections (Tareg *et al.* 2001) • Benzalkonium salts (Reigart and Roberts 1999) • Carbon disulfide (Reigart and Roberts 1999) • Chronic debilitating disease (Clark 2002) • Ciguatoxins (Reigart and Roberts 1999) • Cocaine (Clark 2002) • Codeine (Clark 2002) • Dermatomyositis (Reigart and Roberts 1999) • Genetic deficiency (3% of individuals) (Tareg *et al.* 2001; Clark 2002) • Hepatic parenchymal disease (Clark 2002) • Malnutrition (Clark 2002) • Morphine (Clark 2002) • Pregnancy (Tareg *et al.* 2001) • Oral contraceptives (Tareg *et al.* 2001) • Organic mercury compounds (Reigart and Roberts 1999) • Solanines (Reigart and Roberts 1999) • Some anemias (Tareg *et al.* 2001; Clark 2002) • Succinylcholine (Clark 2002) • Use of gray-top blood collection tubes or those containing fluoride (Clark 2002)
High levels		• Nephrotic syndrome (Clark 2002)

Key Points

- RBC and serum (uninhibited) cholinesterase levels are used to approximate levels in neural tissue, since the latter are impractical to obtain.
- These tests are rarely available in time to guide the emergency treatment decisions. Initial emergency management should therefore be based on clinical assessment.
- When available, test results must be interpreted with caution, because of
    - Interindividual and intraindividual differences in normal cholinesterase levels.
    - Other medical conditions and substances that can alter cholinesterase levels.
    - Laboratory errors.

Progress Check

29. Which of the following statements are true regarding laboratory measurement of cholinesterase inhibitors? (Choose **ALL** correct answers.)

    A. Cholinesterase levels are key to the initial emergency assessment.
    B. Failure to refrigerate blood or serum samples tends to cause a falsely low measurement of cholinesterase level.
    C. With cholinesterase inhibitor toxicity, serum levels of cholinesterase become depressed earlier than RBC levels of cholinesterase.
    D. Serum tests for cholinesterase are more widely available than those for RBC cholinesterase.
    E. None of the above.

    To review relevant content, see "Misconception and Reality," "The Two Types of Cholinesterase Levels" and "Sources of Error in the Measurement of Cholinesterase Levels" in this section.

Direct Measurement of Cholinesterase Inhibitors and Their Metabolic Byproducts

Learning Objectives

Upon completion of this section, you should be able to

- Describe the usefulness of laboratory analysis for the presence of cholinesterase inhibitors themselves and their breakdown products in biological specimens.
- Describe the limitations of laboratory analysis for the presence of cholinesterase inhibitors themselves and their breakdown products in biological specimens.

Introduction

While direct measurements of the actual cholinesterase inhibitors and their metabolic byproducts in body fluids are very accurate, (Clark 2002) their usefulness is limited because

- Each test can only measure one chemical, so it is not useful if you do not know to which one the patient was exposed. (Schenker, Louie *et al.* 1998)
- The results are not available in time to assist in critical treatment decisions. (Mortensen 1986; Schenker, Louie *et al.* 1998; Clark 2002)
- Toxic levels for individual agents have not been established. (Erdman 2004)

However, when these test results are available, they can sometimes help in

- Assessing public health exposure risks to others.
- Providing forensic documentation of poisoning. (Wiener and Hoffman 2004)
- Documenting exposures as a cause of disability.

Note: if such tests are needed, state or federal public laboratories can be consulted.

Cholinesterase Inhibitors That Can Be Measured

Listed below are some of the cholinesterase inhibitors that can be measured in biological fluids.

- Sarin. (Abu-Qare and Abou-Donia 2002; Wiener and Hoffman 2004)
- Some organophosphorus pesticides.
- VX. (Wiener and Hoffman 2004)

Metabolic By-products That Can Be Measured	Alkyl phosphate and phenols (*e.g.,* paranitrophenol (Durham and Hayes 1962)), which are byproducts of organophosphorus compounds • Are sometimes used to quantitate exposure. (Mortensen 1986) • Do not correlate with cholinesterase levels. (Namba 1971) • May be detected for up to 48 hours in urine. • May be positive before clinical signs appear or cholinesterase levels decrease). (Reigart and Roberts 1999) **Note**: Excretion of OP compounds and metabolites is rapid while cholinesterase levels remain depressed for a longer period. (Karalliedde and Senanayake 1989)
Key Points	• While direct measurement of cholinesterase inhibitors or their metabolic byproducts is very accurate, results are not generally available in time to guide acute treatment decisions. • They can sometimes be helpful, however, for forensic and public health purposes.
Progress Check	30. Which of the following are true about direct laboratory measurement of cholinesterase inhibitors and their byproducts? (Choose **ALL** correct answers.) A. Unlike cholinesterase measurements, they are rapidly available to most hospital emergency departments. B. They are only useful, if you know what chemical you are looking for. C. Toxic levels for individual agents have not been established. D. They may be useful for forensic documentation of exposure. E. None of the above. *To review relevant content, see "Introduction" in this section.*

Section 11: Management of the Cholinergic Toxidrome

Three Management Strategies

This section discusses the three primary management strategies for patients with acute cholinesterase inhibitor poisoning.

Management Strategy Number	Topic
1	Prevention of Secondary Exposure
2	Supportive Care
3	Medications

Management Strategy 1: Prevention of Secondary Exposure

Learning Objective

Upon completion of this section, you should be able to

- Describe five key strategies for preventing secondary exposure from patients contaminated with cholinesterase inhibitors.

How Secondary Exposure Occurs

Persons contaminated with toxic cholinesterase inhibiting substances pose a risk to those around them (*e.g.,* prehospital responders, hospital staff, visitors, other patients) that may become secondarily exposed. (Hammond, Merritt *et al.* 1989; Geller, Singleton *et al.* 2001; Horton, Berkowitz *et al.* 2003)

The first priority in managing patients is to prevent secondary exposure and injury to others.

This secondary exposure may occur from direct contact or off-gassing from

- Regurgitated stomach contents containing the ingested chemical. (Geller, Singleton *et al.* 2001; U.S. Occupational Safety and Health Administration 2005)
- The chemical on the victim's skin, hair, or clothing. (Okumura, Suzuki *et al.* 2000; Horton, Berkowitz *et al.* 2003)
- The contaminated vehicle (or its contents) in which the patient was transported.

Example of Secondary Exposure *(Optional Reading)*

A 40-year-old man was brought to the emergency department by a friend approximately 20 minutes after ingesting a concentrated solution of veterinary insecticide. (Geller, Singleton *et al.* 2001) The patient had profuse oral and bronchial secretions, vomiting, bronchospasm, and respiratory distress. The friend also was beginning to show symptoms. Neither had been decontaminated prior to hospital arrival, nor was either decontaminated in the emergency department.

Three emergency department staff exposed to the patient began to show symptoms typical of cholinesterase inhibitor toxicity within an hour of the patient's arrival. All required antidotal treatment. One sickened staff member had to be intubated, and was hospitalized for 9 days. The other two had to be kept in the hospital for 12 hours and overnight, respectively.

MISCONCEPTION: If patients have only been exposed to cholinesterase inhibitor vapor, there is no risk of secondary exposure.

REALITY: Toxic vapors may become trapped in clothing. Subsequent off-gassing has been reported to expose healthcare workers. (Okumura, Takasu *et al.* 1996) At the very least, such patients should have their clothing removed and properly stored in sealed containers.

Five Tactics for Preventing Secondary Contamination

The five key strategies that can be used to control secondary contamination include:

1. Using personal protective equipment (PPE).
2. Carrying out initial assessment and decontamination outdoors or in a room with separate ventilation to the outside (This ventilation should be carried out in such a manner that it does not itself create an exposure risk. Filtering of ventilated air should be considered.).
3. Isolating the patient from other patients, staff, and visitors.
4. Removing the patient's clothing.
5. Decontaminating the patient.

These tactics are well explained in the document, *OSHA Best Practices for Hospital-Based First Receivers of Victims from Mass Casualty Incidents Involving the Release of Hazardous Substances*, (2005) U.S. Occupational Safety and Health Administration. It can be downloaded at no charge from: http://www.osha.gov/dts/osta/bestpractices/html/hospital_firstreceivers.html

Note: It has been said that removing clothing will remove up to 80% of chemical contaminants. However, it has been difficult to verify this, (McMullen 1996) and empirical evidence to support this assertion was not located during the literature search for this case study.

CONTROVERSY: There has been some diversity of opinion as to whether bleach solution (0.5% hypochlorite), water, or soapy water is the best decontamination fluid for use in cases of topical cholinesterase inhibitor exposure.

Some have recommended a 10:1 solution of household bleach (0.5% sodium hypochlorite). The reasoning for this is that this solution is alkaline and organophosphorus compounds hydrolyze faster at an alkaline pH. (Leikin, Thomas *et al.* 2002) One concern about the use of bleach is that it injures skin or eyes, facilitating absorption of the toxicant. Another issue is that bleach solution has to be freshly made daily or it loses its potency. (Levitin, Siegelson *et al.* 2003) Hurst warns against the use of hypochlorite in abdominal or open-chest wounds, on exposed nervous tissue, or in the eye. (Hurst 1997)

Others have reported that water or soapy water is very effective. (Trapp 1985)

PROBABLY MORE IMPORTANT THAN THE SPECIFIC DECONTAMINATION FLUID USED, IS THE RAPIDITY WITH WHICH IT IS APPLIED. (Trapp 1985), (Hurst 1997)

Most data on this subject appears to be derived from studies with chemical warfare nerve agents. See, for example, the table below.

Affect of Decontamination Time Delay on Nerve Agent Survival with Dermal Exposure (Trapp 1985)

Time Delay between Exposure and Initiation of Decontamination	Estimated Survival Rate
2 minutes	80%
5 minutes	30%

Van Hooidonk *et al.* (van Hooidonk, Ceulen *et al.* 1983) in experiments found that in Guinea pigs dermally exposed to VX and Soman, survival was better with soapy water. Interestingly, salad oil was also effective if used promptly. However, mortality after decontamination with each of these solutions increased substantially if decontamination was delayed more than 4 minutes. See the table below.

Mortality in Guinea Pigs Dermally Exposed to VX or Soman *vs.* Decontamination Fluid (van Hooidonk, Ceulen *et al.* 1983)

Decontamination Fluid	Delay Time (min.)	Mortality			
		VX (mg)		Soman (mg)	
		0.25	0.50	5.0	10.0
Bleaching-water*	4	0/8	6/8	6/8	-
Bleaching-water*	10	3/8	-	-	-
Bleaching-water*	30	8/8	-	-	-
Soapy water§	4	0/8	-	0/8	8/8
Soapy water§	10	3/8	-	-	-
Soapy water§	30	7/8	-	-	-
Salad-oil	4	0/8	-	0/8	2/8
Salad-oil	8	5/8	-	-	-
Salad-oil	30	8/8	-	8/8	-

* Concentration not specified
§ Authors indicated that plain water was as effective as soapy water

Key Points

- Patients suffering from cholinesterase inhibitor poisoning can secondarily expose others in their proximity because of contaminated skin, clothing, hair, or emesis.
- Caregivers should be prepared to protect themselves with appropriate personal protective equipment (PPE), isolate such patients, and decontaminate them.
- Rapidity of decontamination can be a crucial determinant of survival in skin exposures.

Progress Check

31. Strategies helpful in reducing secondary exposure include: (Choose **ALL** correct answers.)

    A. The use of personal protective equipment by healthcare workers coming into contact with the patient.
    B. Isolating contaminated patients from other hospital patients.
    C. Removing the patient's clothing.
    D. None of the above.

    To review relevant content, see "Five Tactics for Preventing Secondary Contamination" in this section.

32. Which of the following statements is true about secondary exposure to hazardous substances such as cholinesterase inhibitors: (Choose **ALL** correct answers.)

    A. Healthcare workers can be secondarily exposed to cholinesterase inhibitor poisoning victims due to off-gassing of chemicals on the victims' skin, hair, and clothing.
    B. Patients with skin exposure should be decontaminated with 0.5% hypochlorite (bleach) solution, rather than water.
    C. Indoor decontamination rooms should have independent ventilation to the outside.
    D. Secondary exposure can result from emesis after ingestion of cholinesterase inhibitors.

    To review relevant content, see "How Secondary Exposures Occurs," "Five Tactics for Preventing Secondary Exposures" and "Controversy." in this section.

Management Strategy 2: Supportive Care

Learning Objective

Upon completion of this section, you should be able to

- Identify the most important organ system requiring supportive care in patients suffering from the cholinergic toxidrome.

Introduction

Monitoring and intensive supportive care are critical components of patient management in severe poisoning cases. Monitoring of exposed patients may need to be prolonged because of the possibility of delayed onset of effects from cholinesterase inhibitors.

Importance of Respiratory Support

Death from cholinesterase inhibitor poisoning is usually due to respiratory failure from a combination of: (Zwiener and Ginsburg 1988; Sofer, Tal *et al.* 1989; Reigart and Roberts 1999)

- Bronchoconstriction.
- Bronchorrhea.
- Central respiratory depression.
- Weakness or paralysis of respiratory muscles.

Therefore, early, aggressive respiratory support is a mainstay of treatment, including endotracheal intubation and mechanical ventilation when indicated.

Key Points

- Supportive care plays a critical role in the medical management of the cholinergic toxidrome.
- Aggressive respiratory support is particularly important, since respiratory failure is the usual cause of fatality.

Progress Check

33. The most important aspect of supportive care for cholinesterase inhibitor toxicity is aimed at: (Choose the **ONE BEST** answer.)

    A. The cardiovascular system.
    B. The respiratory system.
    C. The liver and kidneys.
    D. The digestive tract.
    E. None of the above.

    To review relevant content, see "Importance of Respiratory Support" in this section.

Management Strategy 3: Medications

Three First-Line Medications	Three first-line medications, recommended for cholinesterase inhibitor toxicity, will be discussed in detail. • Atropine • 2-PAM • Diazepam

Medications: Atropine

Learning Objectives

Upon completion of this section, you should be able to identify the:

- Mechanism by which atropine counters the effects of the cholinergic toxidrome.
- Clinical findings against which to titrate atropine dosage.
- Preferred routes of administration of atropine.
- Type of cholinesterase inhibitor toxicity that may require extremely high doses of atropine.

Atropine: Mechanism of Action

Muscarinic effects

Atropine works by competitively occupying muscarinic receptor sites, thus reducing the effects of excessive acetylcholine on these sites brought about by cholinesterase inhibition.

Nicotinic effects

Atropine is not thought to have significant effect on nicotinic receptors, and thus does not counteract fasciculations, weakness, or flaccid paralysis. (Leikin, Thomas *et al.* 2002) Thus, even when given sufficient doses of atropine, patients may need artificial ventilation, sometimes for weeks. (Singh, Batra *et al.* 1995)

Note: Although some have suggested that atropine does not cross the blood-brain barrier to any significant extent, (Finkelstein, Kushnir *et al.* 1989) others disagree, having noted prompt resolution of CNS symptoms after its administration. (Sofer, Tal *et al.* 1989; De Wilde, Vogelaers *et al.* 1990)

Diagnostic Use: The "Atropine Challenge"

A number of authors have recommended the "atropine challenge" as an aid to diagnosis.

When given to a normal person who has not been exposed to cholinesterase inhibitors, a 2 mg dose of atropine (0.025-0.050/kg in pediatric cases) causes:

- A dry mouth.
- An increase in heart rate of about 35 beats/minute (which is usually not noticed by the recipient) within 3-5 minutes of an I.V. dose, and a maximal increase in heart rate of about 35-45 beats/minute with I.M. or autoinjector administration, respectively, within about 35-45 minutes (the longer being with I.M. injection).
- Blurred near-vision.
- Dry, hot skin.
- Mydriasis (pupillary dilation).

Most of these effects will dissipate within 4-6 hours, except blurred near-vision which may persist for 24 hours. (Sidell 1997)

It has been suggested that when these physiological changes *do not*

occur with this dose (sometimes referred to as an **atropine challenge**), this is indicative of cholinesterase inhibitor toxicity. (Clark 2002; Erdman 2004)

Cautions

- If miosis (pupillary constriction) is due to direct conjunctival vapor exposure, it is relatively unresponsive to parenteral atropine. (Durham and Hayes 1962; Tareg *et al.* 2001) (Although, it does respond to topical administration).
- In 2-13% of cases of cholinesterase inhibitor toxicity, mydriasis (pupillary dilation) --- rather than miosis (pupillary constriction), (Tsachalinas, Logaras *et al.* 1971; Hayes, van der Westhuizen *et al.* 1978; Aaron and Howland 1994; Erdman 2004)and tachycardia --- rather than bradycardia (3-77% of cases), (Tsachalinas, Logaras *et al.* 1971; Hayes, van der Westhuizen *et al.* 1978; Goswamy, Chaudhuri *et al.* 1994; Nouira, Abroug *et al.* 1994; Singh, Batra *et al.* 1995; Clark 2002; Erdman 2004) may be a presenting signs.
- One author points out that this strategy has never been empirically tested and may not be very sensitive or specific. (Erdman 2004)
- *Parenteral* atropine is not generally recommended for those whose sole manifestation of toxicity is miosis (pupillary constriction). (Sidell 1997)
- Some cases of mild to moderate poisonings may improve with these doses of atropine. Thus, signs of atropinization do not always exclude the presence of cholinesterase inhibitor toxicity. (Clark 2002)

Atropine: Available Forms *(Optional Reading)*

The available forms of atropine are

- Automatic injectors: the U.S. Armed Forces uses autoinjectors, containing 2 mg of atropine. (These atropine autoinjectors are packaged with a 2-PAM autoinjector, called Mark I kits.). (Leikin, Thomas *et al.* 2002)
- Single or multidose vials (0.4-1 mg/ml). (Leikin, Thomas *et al.* 2002; Fernández 2004)
- Ophthalmic ointment (1% in 1g and 3.5 g sizes). (Billups and Billups 2002)
- Ophthalmic solution (1% in 1 ml, 2 ml, 5 ml, 15 ml sizes; 2% in 2 ml size). (Billups and Billups 2002)
- Prepackaged syringes (0.05 mg/ml, 0.5 mg/5 ml, 1 mg/10 ml). (Fernández 2004)
- Reconstituted solution from bulk powder (2 mg/ml in 3 ml syringes) (Geller 1999; Kozak, Siegel *et al.* 2003) Discussed later in this section under the topic, Antidote Stocking.

Caution: One author suggest avoiding large doses of pre-mixed atropine containing alcohol preservatives in children out of concern that alcohol toxicity could complicate the situation. (Schenker *et al.* 1998)

Atropine: Stability of Solution *(Optional Reading)*

There is evidence that atropine solution is very stable and can retain potency long after its expiration date. The table below shows several samples of solution, dating back to World War II, showing its potency. Presumably, the solution was stored in unopened containers (as opposed to multi-dose vials from which any doses had been previously extracted, although this was not explicitly stated. (Schier, Ravikumar *et al.* 2004)

(Optional Reading – Continued)

Atropine Concentration vs. Expiration Date

Expiration Date	Labeled Conc. (µg/ml)	Measured Conc. (µg/ml)	95% Confidence Intervals
Unexpired	400	252	(235-268)
2001	400	290	(272-308)
1999	400	314	(295-333)
1990	400	398	(375-420)
World War II	2,000	1,475	(1,385-1,565)

Note: Tropine, a marker of degradation was not found in substantial amounts in any of the samples.

Data from: Schier JG, Ravikumar PR, Nelson LS, Heller MB, Howland MA, Hoffman RS. Preparing for chemical terrorism: Stability of injectable atropine sulfate. Academic Emergency Medicine. April 2004; 11:329-334.

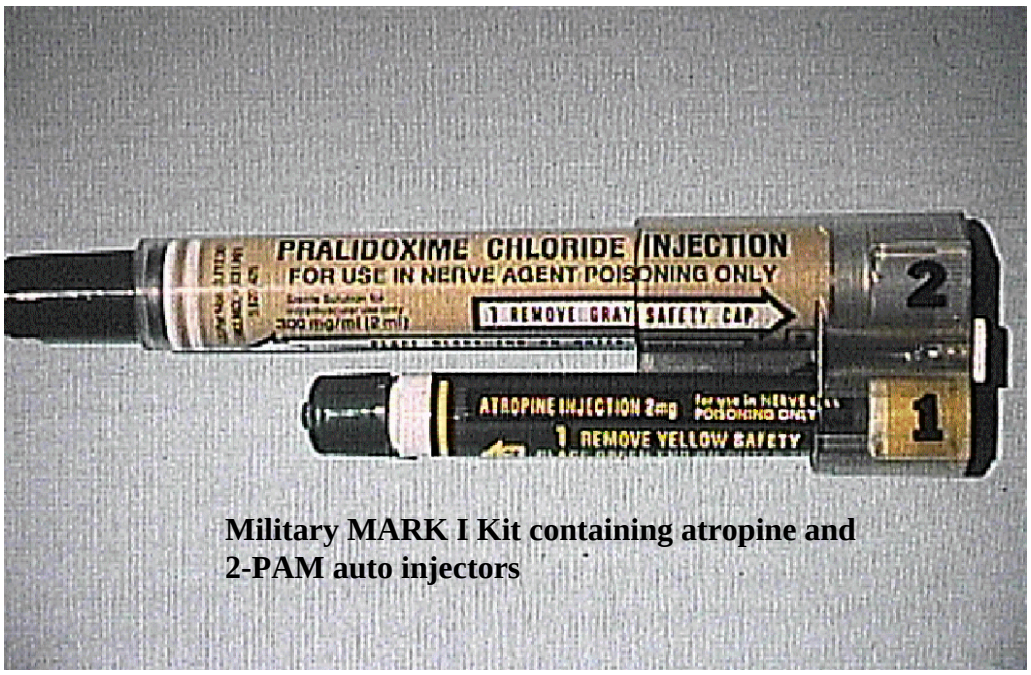
Atropine: Route of Administration

In approximate order of preference, the following routes of administration can be used for the administration of atropine

1. *Intravenous:* bolus, followed by I.V. drip. (Wiener and Hoffman 2004)
2. *Intraosseous: (American Heart Association 2005)* bolus, followed by continuous infusion.
3. *Military MARK I atropine autoinjector:* Although intravenous injection is the preferred route of administration, use of the autoinjector may be more practical in the field, where it can be rapidly administered even through clothing.) Blood levels are achieved more rapidly than by other forms of IM injection. Note that each MARK I kit contains an atropine autoinjector, containing 2 mg of atropine plus another autoinjector containing 600 mg of 2-PAM. (Sidell 1997; Wiener and Hoffman 2004) Pediatric atropine autoinjector syringes are now available in 0.5 mg and 1 mg sizes. (Newmark 2004) (See figures 10-12.)
4. *Intramuscular*: Research for this Case Study did not turn up any comparisons of intramuscular with inhalation routes of atropine administration.
5. *Inhalation*: by nebulized inhalation (Wiener and Hoffman 2004) or via the intratracheal route. The intratracheal route can be used, but absorption is notably less complete and less reliable than the intravenous or intraosseous routes, which are preferred. The optimal intratracheal dose is unknown, but is typically administered in an amount 2-2½ times the intravenous dose. The American Heart Association recommends that the dose be diluted in 5-10 ml water or normal saline. (Reigart and Roberts 1999; American Heart Association 2005; American Heart Association 2005)
6. *Oral*: use has been reported after I.V. administration became

unnecessary. (du Toit, Muller *et al.* 1981)

7. *Ophthalmic:* Anticholinergic eye drops (*e.g.,* atropine or homatropine) have been recommended for severe eye pain caused by miosis (pupillary constriction), and secondary reflex nausea and vomiting, but may result in blurred vision. (Durham and Hayes 1962; Sidell 1997) However, one author questions whether there is enough evidence to recommend this practice. (Wiener and Hoffman 2004)



Military MARK I Kit containing atropine and 2-PAM auto injectors

Figure 10. Military MARK I Kit containing atropine and 2-PAM autoinjectors. Source: U.S. Army Soldier and Biological Chemical Command (SBCCOM).

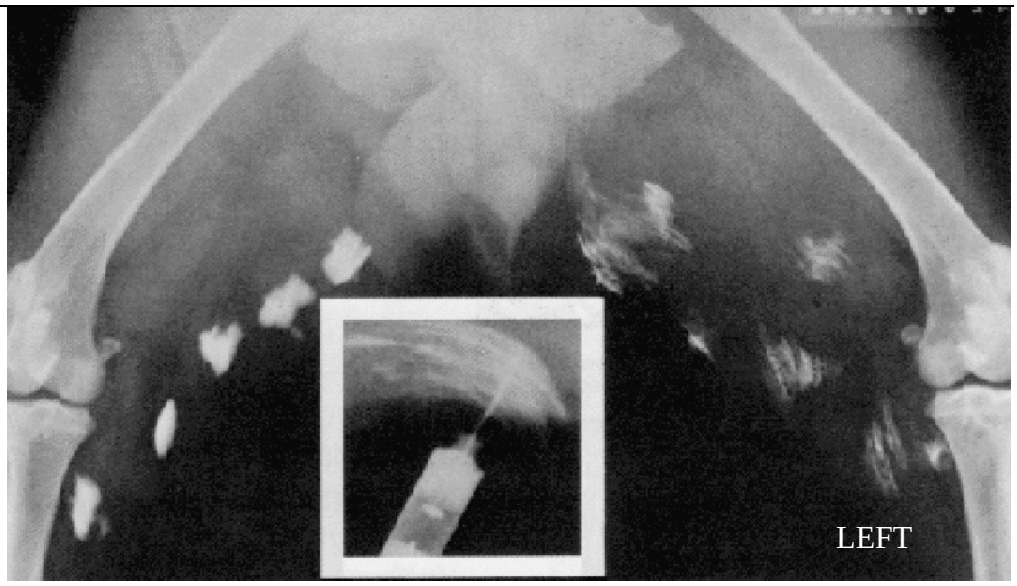


Figure 11. X-ray showing autoinjector effectiveness. The rapid absorption of antidote following automatic injection is enhanced by the degree of tissue dispersion achieved by the autoinjector. The X-ray shows autoinjector doses (on left) compared to standard syringe IM doses (on right). The autoinjector medication is obviously more efficiently diffused into surrounding muscle due to the force with which it is expelled from the injector (as seen in inset photo.) Source: U.S. Army, SBCCOM. (Note: the correct way to view an X-ray is as if the patient was facing you. Thus, the patient's left side is shown on the right.)

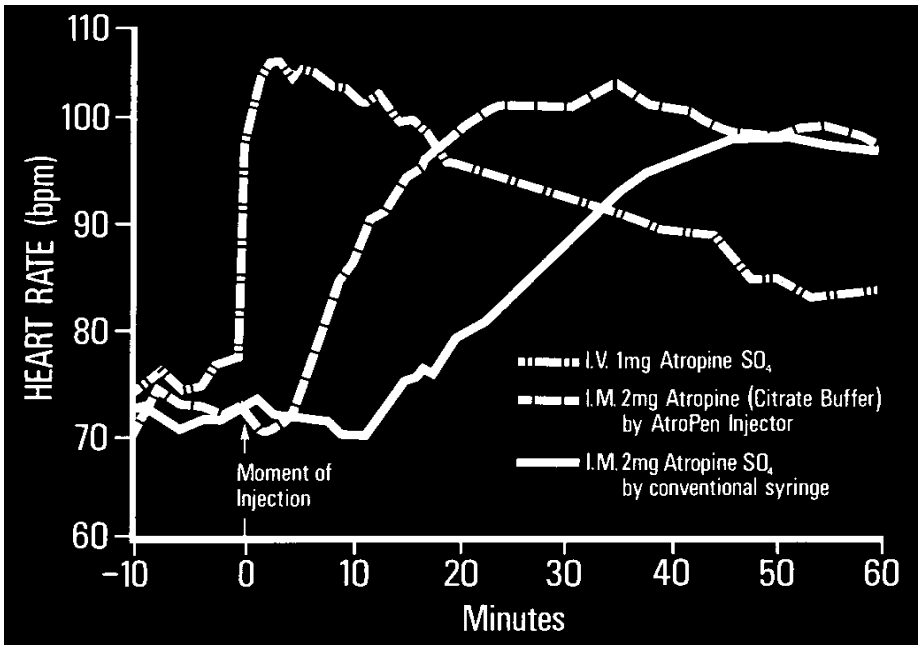


Figure 12. The effects of atropine versus route and method of administration. Source: U.S. Army Soldier and Biological Chemical Command (SBCCOM).

MISCONCEPTION: Atropine should be administered until signs of atropinism appear (tachycardia, pupil dilation, and dry mouth).

REALITY: Although atropine has been used to control other, non-life-threatening effects (*e.g.,* nausea and vomiting) the most crucial end-point for atropine dosage titration is control of *clinically significant* bronchorrhea, bronchoconstriction, (as reflected by level of oxygenation and ease of ventilation) and dangerous bradyarrhythmias or AV-blocks. (Sidell 1997; Reigart and Roberts 1999; Taylor 2001; Erdman 2004; Wiener and Hoffman 2004)

Reasons Why Signs of Atropinism Are Not the Appropriate End Point to Guide Atropine Therapy

Tachycardia should not be used as an end-point, because it sometimes is a nicotinic manifestation of toxicity.

Resolution of *miosis* [Miosis has been defined as pupillary diameter of <3 mm in the dark, along with sluggish or absent response to light. (Gaon and Werne 1955)] should not be used as an end-point, because:

- Miosis (pupillary constriction) from systemic exposure may be a late finding. (Sidell 1997)
- When miosis pupillary constriction) is present, it may be resistant to systemic atropine therapy. (Durham and Hayes 1962; Sidell 1997; Tareg *et al.* 2001)
- Miosis (pupillary constriction) may reflect only localized ophthalmic exposure to vapor without systemic effects. (Durham and Hayes 1962; Sidell 1997)
- Pupils are of normal size in a significant minority of poisoned patients (20% in one series). (Tsachalinas, Logaras *et al.* 1971)
- Toxic patients may present with mydriasis (pupillary dilation) due to occasional dominance of nicotinic effects from cholinesterase inhibitors. (Clark 2002; Erdman 2004)

Atropine Dose

Adults

The most commonly recommended initial doses range from 2 to 6 mg (0.02-0.04 mg/kg). (du Toit, Muller *et al.* 1981)

Authors differ with regards to how frequently these doses should be titrated. Recommended dose intervals vary widely from every 2 to every 30 minutes (Willems 1981; Goswamy, Chaudhuri *et al.* 1994; Singh, Batra *et al.* 1995; Carlton, Simpson *et al.* 1998; Schenker, Louie *et al.* 1998; Tareg *et al.* 2001; Erdman 2004; Fernández 2004) (or 1-3 2 mg autoinjector doses). (Sidell 1997)

After adequate control of secretions, Du Toit *et al.* started their patients with an I.V. maintenance drip of 0.02-0.08 mg/kg/hr titrated to effect. (du Toit, Muller *et al.* 1981) One reported case required 0.5-2.4 mg/kg/hr, I.V. drip, during 5-weeks of treatment. (LeBlanc, Bensen *et al.* 1986)

Some attempts have been made (mostly for nerve agents) to characterize the doses needed according to severity of symptoms. (See the table below for an example.)

The goal of therapy with atropine is to reverse life-threatening signs and symptoms (*i.e.,* respiratory distress), and make the patient more comfortable. Currently it is thought that this does not necessarily require the reversal of all effects of the cholinesterase inhibitor [*e.g.,* miosis (pupillary constriction)].

Generally, in patients with severe symptoms, it is better to give too much atropine than too little. (Sidell 1997)

Children under 12 years of age

Most authors' recommended doses range from 0.05-0.1 mg/kg boluses q 2-30 min. (Zwiener and Ginsburg 1988; Carlton, Simpson *et al.* 1998; Reigart and Roberts 1999; Fernández 2004)

Pediatric atropine autoinjectors (0.5 mg, 1 mg sizes) (Food and Drug Administration 2003) See the chart below.

Patient Weight	**Dose**
15-40 lbs	One 0.5 mg autoinjector dose
40-90 lbs	One 1 mg autoinjector dose

Intravenous drip

Recommendations for I.V. maintenance doses have ranged from 0.2-2.0 mg/hour (0.025 mg/kg/hr in children). (du Toit, Muller *et al.* 1981; Erdman 2004)

Ophthalmic

Topical mydriatics, such as atropine, and homatropine, can provide relief from eye pain and reflex nausea and vomiting. However, these drugs cause blurring of vision, and should be reserved for cases with severe eye pain. (Sidell 1997)

***Warning*:** Hydrocarbons may be used as diluents in liquid formulations of cholinesterase inhibitors. In cases of ingestion, aspiration pneumonitis with acute respiratory distress syndrome may add to the muscarinic respiratory effects of the poison, but is unresponsive to atropine. (Reigart and Roberts 1999)

MISCONCEPTION: Atropine dosage requirements for chemical warfare agent toxicity are greater than for cholinesterase-inhibiting pesticides.

REALITY: The dosage requirements for organophosphorus pesticide toxicity, especially with suicidal ingestions, can be higher by orders of magnitude than is the case for nerve agents.

Total Doses of Atropine in Poisoning with Organo-phosphorus Compounds *(Optional Reading)*

Organophosphorus compounds

The range of atropine doses in the first 12-24 hours stratified by severity is illustrated in the following tables.

Mean atropine dose given during the first 24 hours to 192 adults over 15 years of age (from a sample of 236 cases, ages 1 month to 71 years, 98% of which were poisoned by an organophosphorus insecticide).

Severity of Poisoning	Mean Dose (mg) +/- Standard Deviation Over First 24 hrs
Mild (mild muscarinic signs such as lacrimation, miosis (pupillary constriction), excessive sweating, and hypersalivation).	6.0 +/- 0.7 mg
Moderate (partial or full-blown spectrum of symptoms, but who were breathing unassisted).	26.1 +/- 6.5 mg
Severe (requiring assisted ventilation).	49.8 +/- 4.5 mg

Note: Guidelines used to gauge atropine dosage were documented in only 32 patients. Signs of mild atropine over dosage or dry skin and mucous membranes were used in 18 cases. Tachycardia or mydriasis (pupillary dilation) alone was used in 14 cases.

Extremely High Total Doses of Atropine May be Needed in Suicidal Ingestions of Organophosphorus Compounds *(Optional Reading)*

In cases of suicidal ingestions, atropine doses in the hundreds of milligrams per day have sometimes been needed. (Wyckoff *et al.* 1968; Hopmann and Wanke 1975; du Toit, Muller *et al.* 1981; Golsousidis and Kokkas 1985; Goswamy, Chaudhuri *et al.* 1994; Singh, Batra *et al.* 1995)

- In one reported case, 3,600 mg of atropine was administered in a 24 hour period, with a total dose of 30,730 mg over the patient's 35 days of treatment. Treatment was maintained over a 5 week period at 0.5-2.4 mg/kg/hr, I.V. drip. (LeBlanc, Bensen *et al.* 1986)
- A case reported by Wyckoff (1968) required a total of 1,122 mg of atropine over 10 days. (Wyckoff, Davies *et al.* 1968)
- Willems (1981) reported on some patients who received maintenance atropine doses for up to 20 days. (Willems 1981)

Nerve Agents Require Lower Total Doses of Atropine *(Optional Reading)*

In general, severe nerve agent poisoning requires *lower total doses of atropine* than for organophosphorus compounds. (Sidell 1997)

In severe cases (apneic and unconscious), it may require up to 5-15 mg of atropine to restore consciousness and breathing, and atropine has not been required for more than 2-3 hours. (However, distressing, but not life-threatening effects, such as nausea and vomiting, have required atropine for 6-36 hours afterwards). (Sidell 1997)

In the Tokyo Sarin attack, only 21 of 107 patients who needed atropine required more than 2 mg, and none required more than 9 mg. (Okumura, Takasu *et al.* 1996)

Atropine Doses in Nerve Agent Poisoning *(Optional Reading)*

Adult Atropine Doses for *Nerve Agent* Poisoning

Severity	Signs and Symptoms	Size of titrating doses, q 5-10 min, PRN, I.V.*, or I.M.
Minimal	Isolated miosis (pupillary constriction) and/or rhinorrhea +/- reflex nausea and vomiting.	None‡
Mild	Mild dyspnea, if it does not improve 15-30 after removal from exposure. (Localized sweating, fasciculations after dermal exposure).	0-2 mg‡, or 0-1 MARK 1 kit
Moderate	Moderate to severe respiratory, G.I., or Neuromuscular findings.	2-4 mg, or 1-2 MARK 1 kits
Severe	Apnea, flaccid paralysis, coma, convulsions; severe respiratory distress, or G.I. findings.	6 mg, or 3 MARK 1 kits

*I.V. is the preferred route, when feasible
‡ If < 5 minutes since exposure, increase dose to next level

Data sources: Leikin *et al.* (Leikin, Thomas *et al.* 2002) and Sidell *et al.* (Sidell 1997)

Carbamates Require Lower Doses *(Optional Reading)*

While it is difficult to find information on the actual doses of atropine needed, the severity of carbamate poisoning tends to be less than that for organophosphorus compounds.

The duration of toxicity also tends to be shorter for most patients; on the order of 6-12 hours. (Carlton, Simpson *et al.* 1998)

Warning: Mixed poisoning with organophosphorus compounds and carbamates are common. In one case series of 52 patients, 35% were mixed exposures. (Carlton, Simpson *et al.* 1998)

Atropine: Low Incidence of Adverse Effects

Serious, life-threatening adverse effects from the use of atropine to treat cholinesterase inhibitor toxicity appear to be uncommon. This is even when administered accidentally to children without cholinesterase inhibitor toxicity.

Example: In 268 children accidentally autoinjected with high-dose (up to 17 fold higher than recommended for age) in Israel during the Persian Gulf crises, no fatalities, seizures or life-threatening dysrhythmias were observed. (Amitai, Almog *et al.* 1992)

I.V. atropine has caused ventricular fibrillation in hypoxic animals with nerve agent poisoning. Therefore, it has been recommended that hypoxia be corrected if possible prior to atropine administration. However, atropine should *not be withheld* due to fears of this complication. (Leikin *et al.* 2002)

	Excessive doses of atropine can cause a number of mostly minor anticholinergic symptoms (an exception, perhaps, being delirium), though they can last 24-48 hours. Examples include • Blurred vision (Leikin, Thomas *et al.* 2002) • Dry mouth (Leikin, Thomas *et al.* 2002) • Inability to sweat. (Leikin, Thomas *et al.* 2002) • Muscle fasciculations (Tareg *et al.* 2001) • Mydriasis (pupillary dilation) (Leikin, Thomas *et al.* 2002) • Paralytic ileus (du Toit, Muller *et al.* 1981) • Pyrexia (Tareg *et al.* 2001) • Tachycardia (Leikin, Thomas *et al.* 2002) • Urinary retention (Sidell 1974; Clark 2002; Leikin, Thomas *et al.* 2002) Note: Physostigmine should NOT be administered for these effects in patients with cholinesterase inhibitor poisoning. (Leikin, Thomas *et al.* 2002)
Alternatives to Atropine *(Optional Reading)*	While other antimuscarinic agents (*e.g., scopolamine*) can counteract the effects of cholinesterase inhibitors, their inherent toxic effects in patients who do not have cholinesterase inhibitor poisoning have led to their rejection in favor of atropine. (Sidell 1997; Wiener and Hoffman 2004) *Glycopyrrolate* in doses of 1-2 mg, I.V., (0.025 mg/kg in children) has been suggested as an alternative to atropine, and is said to have fewer CNS side effects. (Clark 2002) However, its use has not been extensively evaluated. (Erdman 2004)

Key Points

- Atropine competitively inhibits the effects of cholinesterase inhibitors at muscarinic, but not nicotinic cholinergic receptors.
- The failure to develop signs of atropinization after a 2 mg dose (0.025-0.050 in pediatric cases) is thought to be very suggestive of cholinesterase inhibitor poisoning, although this has not been empirically tested.
- Atropine should be titrated to achieve control of *clinically significant* bronchorrhea and bronchoconstriction, (as reflected by level of oxygenation and ease of ventilation) and to treat dangerous bradyarrhythmias or AV-blocks.
- Pupil size and heart rate are not reliable end-points for titration of atropine.
- Extremely large doses of atropine may be necessary for poisoning due to suicidal ingestions of organophosphorus pesticides.
- In order of preference, the best routes for administration of atropine are: intravenous, autoinjector, and intramuscular.

Progress Check

34. Atropine counteracts which of the following effects of cholinesterase inhibitor poisoning. (Choose the **ONE BEST** answer.)

    A. Muscarinic effects.
    B. Nicotinic effects.
    C. Muscarinic and nicotinic effects.
    D. None of the above.

    To review relevant content, see "Atropine: Mechanism of Action" in this section.

35. Which of the following is the best end-point for titration of atropine dosage? (Choose the **ONE BEST** answer.)

    A. Pupillary dilation
    B. Development of heart-rate >100/min
    C. Development of blood pressure > 120/80
    D. Skin flushing
    E. None of the above.

    To review relevant content, see "Misconception/Reality" in this section.

36. In cases of suicidal insecticide organophosphorus cholinesterase inhibitor ingestion: (Choose **ALL** correct answers.)

    A. Atropine should be given intravenously, but if an I.V. line cannot be established, it is better to give it I.M. than by autoinjector.
    B. Extremely high doses of atropine may be required
    C. Atropine dosage requirements are less than that needed for nerve gas poisoning.
    D. Atropine should not be used unless miosis (pupillary constriction) is present
    E. None of the above.

    To review relevant content, see "Extremely High Total Doses of Atropine May be Needed in Suicidal Ingestions of Organophosphorus Compounds" in this section.

37. Which of the following statements are true about the route of administration of atropine? (Choose **ALL** correct answers.)

    A. The intravenous route is preferred.
    B. Intramuscular injection provides more rapid onset than the use of an atropine autoinjector.
    C. Atropine can be administered by the intraosseous route.
    D. Atropine can be administered by the intratracheal route.
    E. None of the above.

*To review relevant content, see "*Atropine: Route of Administration*," in this section.*

Medications: 2-PAM (2-Pyridine Aldoxime Methylchloride) (Pralidoxime)

Learning Objectives

Upon completion of this section, you will be able to:

- How 2-PAM works as an antidote.
- How 2-PAM influences the body's response to atropine and vice-versa.
- What "aging" is, as it relates to 2-PAM, and how the process can affect response to treatment.
- Situations that delay the onset of toxicity and aging of cholinesterase inhibitors.
- Reasons for treatment failure with 2-PAM.
- The recommendations for use of 2-PAM in carbamate poisoning.

Introduction

2-PAM (2-pyridine aldoxime methyl chloride) --- also called **pralidoxime** --- is one of a class of chemicals, called **oximes** that reverse the binding of cholinesterase inhibitors with acetylcholinesterase. There is some controversy about the efficacy of 2-PAM and about the correct dosing.

2-PAM is currently the only FDA approved oxime in the United States, and will be the only one discussed specifically in this case study. (Obidoxime is the agent commonly used in much of Europe and other parts of the world.) (Erdman 2004)

Some evidence suggests that 2-PAM may be a safer drug. In a 1998 human study, half of the 12 patients treated with obidoxime died, and 3 developed liver complications (two of which were among the fatalities). None of the 8 patients receiving 2-PAM developed hepatotoxicity, and all survived. (Balali-Mood and Shariat 1998)

How 2-PAM Works

2-PAM attaches to the site where the cholinesterase inhibitor has attached to and blocked cholinesterase. 2-PAM then attaches to the cholinesterase inhibitor and removes it from cholinesterase, allowing the enzyme to work normally again. This is sometimes referred to as "regeneration" of cholinesterase. The molecular details of how this happens are described in the following Optional Reading.

Aging

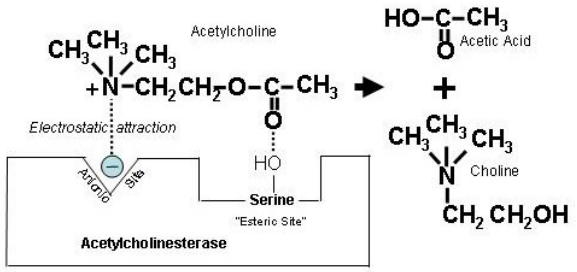
After a period of time, some cholinesterase inhibitors can form a permanent bond with cholinesterase that cannot be reversed by oximes such as 2-PAM. This happens in a process called "aging." Carbamates do not age.

How Long Does It Take for Aging to Occur?

The time it takes for a cholinesterase inhibitor bond to age varies. Some examples are (Wiener and Hoffman 2004)

- Soman – 2 minutes
- Sarin – 5 hours
- VX – over 40 hours

Early studies suggested that 2-PAM had to be given within 48 hours or aging would prevent it from working. However, Howland (1994) indicates these studies were later proved to be flawed methodologically, and subsequent evidence suggests that 2-PAM can be effective long after 48 hours, depending on the specific organophosphorus compound involved.

	(Howland and Aaron 1994) Furthermore, as discussed further below, delayed onset of poisoning can result in delay of aging for days or even weeks. (Clark 2002) More information on what happens at the molecular level during aging is discussed in the Optional Reading below.
Reasons for Delayed Onset of Toxicity and Aging, and Need for Extended Treatment with 2-PAM	In addition to general differences in chemical structure, three situations in particular are noteworthy for causing delayed onset of cholinesterase inhibition, as well as of aging, and require prolonged treatment with 2-PAM (and, atropine as well). This situation also prolongs the period when 2-PAM is effective (that period before aging occurs). Fat soluble organophosphorus compounds, such as fenthion and chlorfenthion can redistribute from fat stores over time. They will not have aged and can continue to re-inhibit cholinesterase for days. (Howland 2002) Some cholinesterase inhibitors have a delayed onset because they must first be metabolically converted to the active, toxic ingredient. Examples include parathion, which is converted to paraoxon, and malathion, which is converted to malaoxon. (Clark 2002; Howland 2002) Delayed onset may also occur with dermal exposure. (Sidell 1997; Howland 2002)
2-PAM: Mechanism of Action *(Optional Reading)*	Before describing 2-PAM's mechanism of action, it is helpful to understand exactly how cholinesterase breaks down acetylcholine, and how cholinesterase inhibitors prevent this from happening. An important phenomenon is the process called "aging" which can prevent 2-PAM from working.
How Acetyl-cholinesterase Normally Works *(Optional Reading)*	 **Figure 13.** How the positively charged nitrogen in the acetylcholine molecule is attracted to the ionic site on acetylcholinesterase, and hydrolysis is catalyzed at the esteric site to form choline and acetic acid.
How Cholinesterase Inhibitors Work *(Optional Reading)*	Figures 14-18 below show how a cholinesterase inhibitor (in this case, a nerve agent) attaches to the serine hydroxyl group on acetylcholinesterase. This prevents acetylcholine from interacting with the cholinesterase enzyme and being broken down.

How Cholinesterase Inhibitors Work (Optional Reading - *continued*)

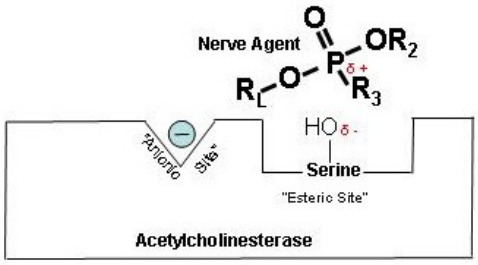


Figure 14. Partially electropositive phosphorus is attracted to partially electronegative serine.

δ + Indicates that phosphorus is partially electropositive.

δ – Indicates that oxygen is partially electronegative.

Diagrams modified from Wiener, S. W., and R. S. Hoffman. "Nerve Agents: A Comprehensive Review." *Journal of Intensive Care Medicine* 19, no. 1 (2004): 22-37.

How Cholinesterase Inhibitors Work. (Optional Reading - *continued*)

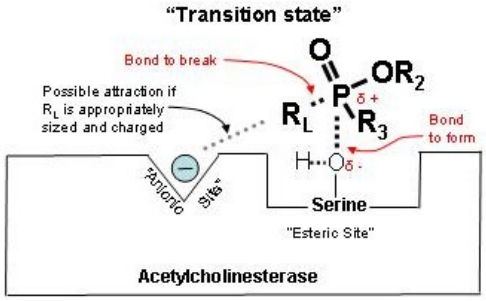


Figure 15. Transition state showing which bonds break and which ones form.

How Cholinesterase Inhibitors Work. (Optional Reading - *continued*)

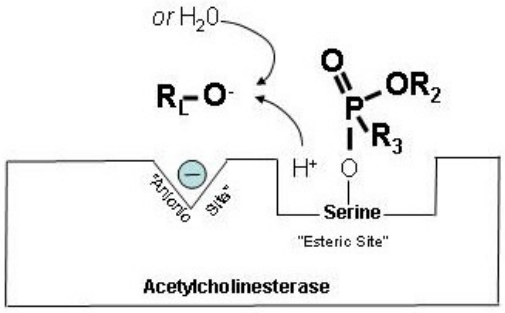


Figure 16. Cholinesterase inhibitor attached to acetylcholinesterase preventing the attachment of acetylcholine.

How Cholinesterase Inhibitors Work: Aging (Optional Reading - *continued*)

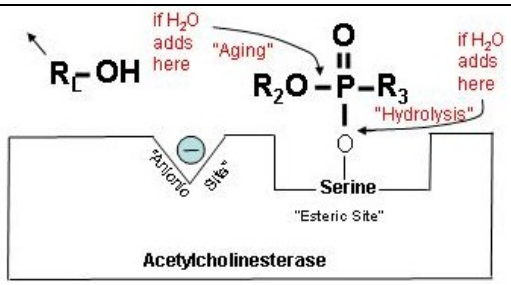


Figure 17. Cholinesterase is blocked, but it can:

- Hydrolyze to original state (slow).
- Regenerate with an oxime (fast).
- "Age" (cannot regenerate).

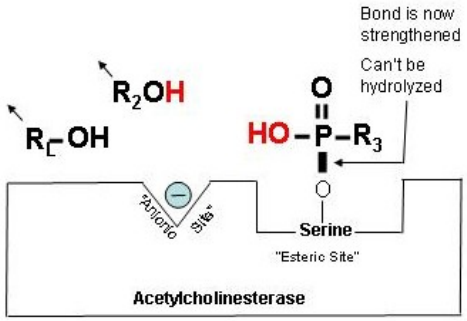


Figure 18. The "aged" bond

- After addition of **H_2O** to the P- R_3 bond. Prior to aging, R_2 was pulling the electrons away from "P". Upon its being removed during the aging process, these electrons are shared with "O"-Serine, strengthening its bond, so that it can no longer be hydrolyzed.

How 2-PAM Works at the Molecular Level *(Optional Reading)*

Figures 19-21 below show that when the antidote, 2-PAM, is administered, the positively charged quaternary nitrogen on 2-PAM is attracted to the anionic site of acetylcholinesterase. 2-PAM then reacts with and removes the cholinesterase inhibitor. However, this cannot occur after aging has occurred.

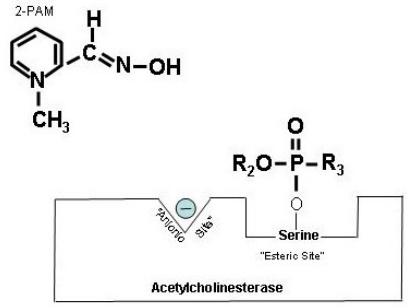


Figure 19. How 2-PAM works.

How 2-PAM Works (Optional Reading – Continued)

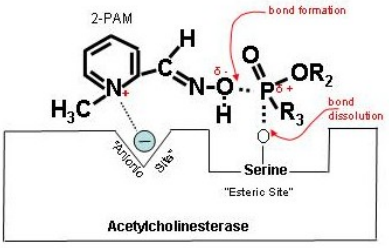


Figure 20. Partially electropositive nitrogen on 2-PAM is attracted to electronegative anionic site on cholinesterase.

How 2-PAM Works at the Molecular Level (Optional Reading – Continued)

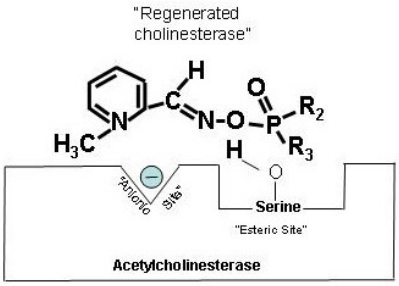


Figure 21. Regenerated cholinesterase.

2-PAM in Carbamate Toxicity

Carbamate insecticides have similar cholinesterase inhibiting toxicity as organophosphorus compounds and nerve agents.

However, the carbamate-cholinesterase bond spontaneously hydrolyzes with a half-life of 1-2 hours, inactivating the poison, with clinical recovery occurring in several hours, and only rarely in >24 hours. Because of this, in the past, patients were not treated with 2-PAM. However, its use in carbamate toxicity can reduce the clinical severity.

The carbamate-cholinesterase bond does not age. (Howland 2002)

Furthermore, as noted previously, mixed poisonings with organophosphorus compounds and carbamates are common. In one case series of 52 patients, 35% were mixed exposures. (Carlton, Simpson *et al.* 1998)

MISCONCEPTION: 2-PAM is contraindicated in carbamate poisoning.

REALITY: 2-PAM, if administered alone, has been shown to worsen outcome in only one type of carbamate --- carbaryl. However, when atropine is co-administered with 2-PAM (which should always be done), survival is improved.

2-PAM in Carbamate Toxicity

2-PAM was once thought to be contraindicated in carbamate toxicity. This was apparently based on animal data from the study of a single carbamate, carbaryl, which was generalized to all carbamates. In this study it was found that carbaryl toxicity was worsened when treated with 2-PAM alone. (Dawson 1994)

Harris *et al.* showed that the protective ratio (defined as the LD_{50} with treatment/LD_{50} without treatment) of 2-PAM alone for carbaryl was 0.6 as compared to a protective ratio of 6.6 from treatment with atropine alone. (However, when atropine and 2-PAM were given together the protective ratio was 3.5). (See table below abstracted from Harris *et al.*) (Harris, Talbot *et al.* 1989)

Effectiveness of atropine and 2-PAM against carbaryl toxicity in rats

Treatment	LD_{50}* in mg/kg, I.P. (95% confidence limits)	Protective Ratio**
None	69.9 (50.0-105.0)	1.0
2-PAM	39.4 (28.6-57.1) $p<0.05$ compared to no treatment	0.6
Atropine	460 (335.0-669.0) $p< 0.05$ compared to all other treatments	3.5
2-PAM + Atropine	244 (180.0-339.0) $p<0.05$ compared to all others	3.5

*LD_{50}: The dose that will kill 50% of the subjects

** Protective Ratio: LD_{50} with treatment/LD_{50} without treatment

In vitro and *in vivo* animal studies have shown that oximes, including 2-PAM, either reduce or have a neutral effect on the toxicity of carbamates other than carbaryl. (Natoff and Reiff 1973)

2-PAM: Availability *(Optional Reading)*

Supplied in 20 ml vial containing 1 g powder, ready for reconstitution with sterile water for injection, (Howland 2002) and in autoinjectors containing 600 mg. (Sidell 1997)

Obtain Blood Prior to Treatment

Before giving 2-PAM, a blood sample (heparinized) should be drawn for RBC and serum cholinesterase analysis in case it is needed later, as the antidote tends to reverse cholinesterase depression. (Reigart and Roberts 1999)

2-PAM: Dosing	According to the pharmaceutical manufacturer, the recommended loading dose is: ***Adults*** 1-2 g in 100 ml of 0.9% NS, IV, over 15-30 min. (Howland 2002) ***Pediatric*** The pediatric dose is 20-40 mg/kg, IV over 30 min. (Howland 2002) These initial doses can be repeated in 1 hour if muscle weakness and fasciculations are not relieved. Thereafter, additional doses may be needed every 3-8 hours, as long as signs of poisoning recur. (Howland 2002) **Note**: Because 2-PAM is eliminated by the kidneys, dose should be reduced in patients with renal insufficiency. (Carlton, Simpson *et al.* 1998) **Note**: In case of pulmonary edema, the dose can be given in a 5% solution (concentrations >35% w/v produce muscle necrosis in animals). (Howland 2002)
Controversy Regarding 2-PAM Dose *(Optional Reading)*	Currently, despite manufacturer's recommendations, there is controversy over the appropriate dosing of 2-PAM. The dose recommendations listed above were designed to achieve a serum level of at least **4 µg/ml**, a level that has been shown to provide protection from a sarin analogue in the cat model. (Howland 2002; Wiener and Hoffman 2004) Some have argued that this has never been replicated with other cholinesterase inhibitors nor with other species. (Wiener and Hoffman 2004) Others point out that this does not take into account the dose and route of exposure. (Wiener and Hoffman 2004) Balali-Mood and Shariat (1998) found that 2-PAM improved outcome and was not associated with serious side effects in eight patients treated with a loading dose of 30 mg/kg followed by a maintenance dose of 8 mg/kg/hr. (Balali-Mood and Shariat 1998) Recent *in vitro* studies suggest that a much higher level is actually needed. Studies with the cholinesterase inhibitor, paraoxon showed that a 20% reactivation of cholinesterase was achieved with a serum concentration of 10 µg/ml and 70% with 17 µg/ml. (Howland 2002)

Need for Maintenance I.V. Infusion	Several authors have provided evidence that following a bolus of 2-PAM, serum levels fall below 4 µg/ml within 90-120 min, and that maintenance infusions can maintain effective therapeutic levels. (Howland 2002; Wiener and Hoffman 2004) However, there has been no randomized controlled comparison between intermittent bolus and continuous infusion therapy. (Wiener and Hoffman 2004) Based on their interpretation of the available data, Howland (Howland 2002) as well as Wiener and Hoffman (Wiener and Hoffman 2004) recommend 1. an initial dose of **1-2 g (20-40 mg/kg in children to a maximum of 1 g)** 2. followed by a continuous infusion at **500 mg/hr (10-20 mg/kg/hr)**
2-PAM: Duration of Treatment	The duration of treatment is also controversial, and there are not good data supporting any one approach. However, a reasonable approach is to continue treatment until at least 24 hours after symptoms resolve. (Wiener and Hoffman 2004) Some have suggested using serial RBC cholinesterase measurements as a guide to 2-PAM therapy. (Erdman 2004) Resolution of all signs and symptoms can occur even when up to 50% of cholinesterase is still inhibited. At this stage, patients may still benefit from further reactivation of cholinesterase by the continued administration of 2-PAM. (Howland 2002)
Reasons for Apparent Failure to Respond to 2-PAM	In patients who do not respond with clinical improvement, there are several possibilities: • Active cholinesterase inhibitor absorption or redistribution (*e.g.,* from adipose tissue) is continuing to occur. • Aging has already occurred. • An inadequate dose was given. 2-PAM treatment should be continued in many such situations, as it may be difficult to distinguish the reasons for treatment failure.
2-PAM: Synergism with Atropine	2-PAM and atropine are synergistic in their effects. (Howland and Aaron 1994) Studies of organophosphate toxicity in rabbits have shown that effectiveness of atropine plus 2-PAM is 35 times greater than with atropine alone. (O'Leary, Kunkel *et al.* 1961)

2-PAM: Adverse Effects	Adverse effects at therapeutic doses are minimal and usually do not occur unless total doses are exceptionally high (>400 µg/ml). Transient dizziness, blurred vision, and diastolic hypertension may be related to rate of administration. (Howland 2002) *Rapid* IV injection has produced: (Tareg *et al.* 2001) • Hypertension. • Laryngospasm. • Tachycardia. • Muscle rigidity. • Transient neuromuscular blockade. Infusion of >200 mg/min in adults can rarely cause respiratory or cardiac arrest. (Howland 2002)
Controversy Regarding What Receptor Sites are Affected by 2-PAM *(Optional Reading)*	While 2-PAM's most noted effects are on nicotinic receptors, there is controversy as to whether it also affects muscarinic receptors. (Karalliedde and Senanayake 1989; Howland and Aaron 1994; Erdman 2004)
Does 2-PAM Cross the Blood-Brain Barrier? *(Optional Reading)*	Because 2-PAM is a quaternary nitrogen compound, it would not be expected to cross the blood-brain barrier. However, prompt resolution of coma and CNS disturbances has been noted in case reports after its administration. (Funckes 1960; Brachfeld and Zavon 1965; Howland and Aaron 1994)
Controversy Regarding 2-PAM Efficacy	As with many of the treatments used for poisoning, (Buckley, Karalliedde *et al.* 2004) there is a lack of high quality evidence to document the effectiveness of 2-PAM. Thus, management of these cases is based largely on knowledge from case reports and expert opinion. Most of the evidence for 2-PAM effectiveness comes from (Funckes 1960; Quinby and Clappison 1961; Durham and Hayes 1962; Namba, Nolte *et al.* 1971; Lotti and Becker 1982; Xue, Ding *et al.* 1985; Hayes and Laws 1991; Howland and Aaron 1994; Sidell 1997; Eddleston, Szinicz *et al.* 2002; Kassa 2002; Buckley, Karalliedde *et al.* 2004; Erdman 2004) • Anecdotal and case (or case series) reports. • Animal data. • *In vitro* experiments.
Factors Needing Control in Studies on 2-PAM *(Optional Reading)*	Several factors need to controlled when assessing the effectiveness of cholinesterase-regenerating antidotes (oximes) such as 2-PAM. ***Adequacy of dosing*** If insufficient doses are used, 2-PAM's effectiveness is compromised.

(Johnson, Vale *et al.* 1992; Worek, Backer *et al.* 1997; Leikin, Thomas *et al.* 2002) The amount needed may vary depending on the specific cholinesterase inhibitor involved. (Eddleston, Szinicz *et al.* 2002)

The specific cholinesterase inhibitor involved

2-PAM works with some but not others. (Eddleston, Szinicz *et al.* 2002) So, for example, it is very effective with parathion, less effective with Dichlorvos, and had no apparent effect on dimethoate. (Xue, Ding *et al.* 1985)

The time since exposure

Some cholinesterase inhibitors undergo an "aging" process after which 2-PAM is no longer effective. For these substances, the time period for this aging to occur varies. (Karalliedde and Senanayake 1989; Eddleston, Szinicz *et al.* 2002; Leikin, Thomas *et al.* 2002; Wiener and Hoffman 2004)

Published Attempts at Controlled Human Studies with 2-PAM ***(Optional Reading)***

Several attempts have been made to carry out controlled prospective human studies on the effectiveness of 2-PAM. Unfortunately, they all suffer from methodological problems, as detailed below. These design flaws have made it difficult to draw any solid empirical conclusions on 2-PAM's effectiveness.

Studies 1 and 2

Eddleston *et al.* (2003) were able to find only 2 published, randomized controlled human trials of 2-PAM. Both of these studies concluded that 2-PAM was associated with a worse outcome, and they have been used to argue that the antidote should not be used. However, these studies were flawed by methodological problems. In particular, the factors needing control as described above were not controlled, and important design information was missing (*e.g.,* randomization procedures, patient weight used for dosing). (Eddleston, Szinicz *et al.* 2002)

Study 3

Another controlled study was reported by Balali-Mood and Shariat. (1998) (Balali-Mood and Shariat 1998) Patients were admitted within 6 hours and assigned to one of three treatment groups: 1) atropine; 2) atropine + obidoxime; and 3) atropine + 2-PAM. Their 2-PAM dosing regimen of 30 mg/kg loading then 8 mg/kg maintenance was adequate. Although the atropine + 2-PAM had more respiratory complications and longer hospital stays, there was no mortality in this group.

In contrast the mortality was 12% and 50% in the atropine-only and atropine + obidoxime groups, respectively. It is of interest that in the latter group, 3 patients developed hepatitis, and 2 of them died from hepatic insufficiency.

There is no documentation that patients were randomly assigned to the treatment groups (although there were no significant differences in their major presenting clinical findings, including RBC cholinesterase levels). Although more than 10 different organophosphate cholinesterase inhibitors were involved, no attempt was documented to control for the different types (*e.g.,* by multiple regression statistical techniques that can control for more than one variable at a time). In addition, the sample sizes for this study were small.

Study 4

De Silva *et al.* reported that during a period when 2-PAM was not available to them in Sri Lanka, they found that patients fared no worse with atropine alone than with previous patients that had received atropine + 2-PAM. (de Silva, Wijewickrema *et al.* 1992)

However, their conclusions were called into question because of inadequate dosing. Furthermore, patients were included in the study if they had been seen within 24 hours of ingestion. However, about 70% of their patients had ingested dimethylated compounds which tend to age within 12 hours. (Johnson, Vale *et al.* 1992; Eddleston, Szinicz *et al.* 2002)

Key Points

- 2-PAM attaches to cholinesterase inhibitors that have blocked cholinesterase and removes them from the enzyme, thereby reactivating it.
- Some cholinesterase inhibitors after a time will form a permanent bond with cholinesterase in a process called aging, after which 2-PAM is no longer effective.
- Factors which can delay the onset of toxicity and prolong the period before aging occurs include
  - Toxicity from fat soluble organophosphorus compounds, such as fenthion and chlorfenthion which can redistribute from fat stores over time.
  - Toxicity from chemicals, such as parathion and malathion, that must be first metabolically converted to their active forms.
  - Dermal exposure, which can delay absorption and toxicity for up to 18 hours.
- 2-PAM should be given in conjunction with atropine, with which it has a notable synergistic effect.
- Although it has been suggested that 2-PAM was absolutely contraindicated in carbamate poisoning, data are lacking to support this recommendation.
- 2-PAM treatment failures can occur when
  - An inadequate dose has been given.
  - Aging has already occurred.
  - Active cholinesterase inhibitor absorption or redistribution (*e.g.,* from fat tissue) is continuing to occur.

Progress Check

38. Which of the following statements are true about 2-PAM (Choose **ALL** correct answers.)

    A. It works by attaching to cholinesterase inhibitors that have blocked cholinesterase, and removing the cholinesterase inhibitor.
    B. It will not work after "aging" has occurred.
    C. Its effects are multiplied when atropine is co-administered.
    D. None of the above.

    To review relevant content, see "How 2-PAM Works," "Aging" and "Misconception-Reality" in this section.

39. Which of the following delay the onset of cholinesterase inhibitor toxicity as well as the onset of aging (and therefore prolong the period during which 2-PAM is still effective)? (Choose **ALL** correct answers.)

    A. Dermal exposure.
    B. Exposure to cholinesterase inhibitors which high fat solubility.
    C. Exposure to cholinesterase inhibitors that do not become toxic until metabolically converted to their active ingredients.
    D. None of the above.

    To review relevant content, see "Reasons for Delayed Onset of Toxicity and Aging, and Need for Extended Treatment with 2-PAM" in this section.

40. Which of the following statements are true about the treatment of carbamate poisoning? (Choose **ALL** correct answers.)

    A. 2-pam is contraindicated in all cases of carbamate poisoning.
    B. 2-pam *plus* atropine has been shown to worsen the outcome in carbamate poisoning due to carbaryl when compared to giving no antidote.
    C. Atropine alone is contraindicated *in all cases* of carbamate poisoning.
    D. None of the above.

    To review relevant content, see "2-PAM in Carbamate Toxicity" in this section.

41. Causes of failure with 2-PAM treatment include: (Choose **ALL** correct answers.)

    A. Administration of inadequate doses.
    B. Aging has already occurred.
    C. Active cholinesterase inhibitor absorption or redistribution (*e.g.*, from fat tissue) is continuing to occur.
    D. None of the above.

    To review relevant content, see "Reasons for Apparent Failure to Respond to 2-PAM" in this section.

Medications: Diazepam

Learning Objectives

Upon completion of this section, you should be able to

- Describe why seizure prevention and control is important in the management of the cholinergic toxidrome.
- Describe the difference in the risk of seizures between adults and pediatric cases of the cholinergic toxidrome.

MISCONCEPTION: Brain damage from cholinesterase inhibitors reflects a direct toxic effect on neuronal tissue.

REALITY: Current thinking is that brain damage results from seizures triggered by cholinesterase inhibitors.

Introduction: Diazepam for Seizures

Incidence of seizures

- While seizures due to cholinesterase inhibitor toxicity are uncommon in adults, they are common in pediatric cases. (Sofer, Tal *et al.* 1989; Tareg *et al.* 2001)
- They can also be an important problem in adults with high-dose *nerve agent* intoxication. (Romano, McDonough *et al.* 2001)
- The mechanism of convulsion activity is unclear but may involve effects on GABAnergic, glutamanergic, noradrenergic, dopaminergic, and serotonergic systems. (Sidell 1997)

CNS damage appears to be a direct effect of seizure activity

- Current thinking is that CNS damage from cholinesterase inhibitors is not a direct toxic effect, but is due to seizure activity. (Lotti 1992; Somani, Solana *et al.* 1992; Sidell 1997; Clegg and van Gemert 1999) At the Workshop on Convulsions and Related Brain Damage Induced by Organophosphorus Agents, held at Aberdeen Proving Ground in Maryland, it was generally agreed that brain lesions did not occur if convulsions lasted less than 45 minutes, and that brain damage was found if convulsions lasted longer than 45 minutes. (Sidell 1997)

Administration of diazepam appears to increase survival and reduce CNS damage in nerve agent poisoning

- Seizures may not be adequately controlled with atropine and 2-PAM alone. (Schenker, Louie *et al.* 1998)
- However, evidence suggests that with significant poisoning, the administration of diazepam is effective, and (even in the absence of seizures) increases survival and reduces CNS damage, and cardiac dysfunction. (Sidell 1997; Erdman 2004; Wiener and Hoffman 2004)
- Currently, the administration of diazepam is recommended to treat or prevent these seizures. (Sidell 1997; Leikin, Thomas *et al.* 2002; Erdman 2004)

Indications	Current recommendations are for the administration of diazepam for seizures due to nerve agent poisoning and even for severe toxicity (severe respiratory distress or neuromuscular signs) in the absence of seizures. (Sidell 1997; Leikin, Thomas *et al.* 2002)
Dose (Sidell 1997; Leikin, Thomas *et al.* 2002)	***Adult*** **5-10 mg, IV**, q 5-10 min (1, 10 mg autoinjector, q10 min x 3 maximum) ***Pediatric*** ***0.2 mg/kg, IV**, q 5-10 min.*
Key Points	• CNS damage from cholinesterase inhibitor poisoning is currently thought to be due to seizure activity rather than a direct toxic effect. • Prevention and treatment of seizures with diazepam is an important aspect of patient management. • Seizures are more common in pediatric poisoning with cholinesterase inhibitors.
Progress Check	42. Which of the following statements is true about the use of diazepam for acute cholinesterase inhibitor toxicity? (Choose **ALL** correct answers.) A. Diazepam is recommended for severe nerve agent poisoning even in the absence of seizures. B. Current thinking is that CNS damage from acute poisoning with cholinesterase inhibitors is due to seizure activity rather than from a direct toxic effect on brain tissue. C. The likelihood of seizures in acute cholinesterase inhibitor poisoning is greatest in pediatric cases and in severe cases of nerve agent poisoning. D. None of the above. *To review relevant content, see "Introduction" in this section.*

Antidote Stocking (*Optional Reading)*

Learning Objectives ***(Optional Reading)***	Upon completion of this section, you should be able to • Identify what antidotes should be stocked for the treatment of patients, or mass casualties involving cholinesterase inhibitor poisoning. • Describe what local agencies to contact for information about accessing the Strategic National Stockpile.
MISCONCEPTION: Hospitals have adequate stocks of antidotes to treat most cases of cholinesterase inhibitor toxicity. **REALITY:** Repeated studies have reported that many hospitals lack sufficient antidote stores to treat even one severe case of cholinesterase inhibitor poisoning, much less enough for a multiple casualty event or terrorist attack.	
Inadequacies in Antidote Stocking ***(Optional Reading)***	***2-PAM*** Numerous studies have documented the failure of hospitals to stock enough 2-PAM to treat one patient, much less to handle a mass casualty event. (Parker, Dart *et al.* 1990; Chyka and Conner 1994; Dart, Stark *et al.* 1996; Woolf and Chrisanthus 1997; Teresi and King 1999; Treat, Williams *et al.* 2001; Kaji and Lewis 2004) ***Atropine*** Currently, data on hospital stocking of atropine are lacking. However, even one severe case of toxicity from an organophosphorus compound can require the amounts of atropine that would exceed the stores in most communities. [The highest reported dosage requirement was for 3,600 mg in a 24 hour period for a suicidal ingestion, with a total dose of 30,730 mg over the patient's 35 days of treatment. (LeBlanc, Bensen *et al.* 1986)] ***The need to assess hospital stores of antidotes*** Because inadequacies in hospital stocking of antidotes appear to be widespread, community disaster planners need to inventory local/regional stocks and ensure they are adequate.
Atropine from Bulk Powder ***(Optional Reading)***	Because of the high doses required for some cases of organophosphate poisoning, and because of the potential for mass casualty incidents involving pesticides and nerve agents, rapid access to large amounts of atropine may be critical. To address this problem, protocols have been developed for the reconstitution of high-concentration atropine from bulk powder. ***Time required and cost.*** Using such an approach, a single pharmacist can reconstitute one hundred 6 mg syringes of atropine within about a half-hour, at a cost of as little as $11 (versus $5,000 for prefilled syringes). ***Storage characteristics.***

	Even when stored at up to 45°C (113°F) 87% of the atropine sulfate reconstituted from bulk power was still undegraded, pathogen-free, and without tropic acid (an expected degradation product) after 8 weeks. (Geller, Lopez *et al.* 2003; Kozak, Siegel *et al.* 2003) **Note:** Few studies have been carried out to assess how many hospitals keep adequate stocks of atropine on hand for cholinesterase poisoning. One survey in a major metropolitan area in the year 2000 found that while 1,213.237 grams were available city-wide, only 1 of 21 area hospitals had a 3 g supply of the antidote on hand. (Keim, Pesik *et al.* 2003) Another study of 38 hospitals reported that atropine was one of the "conspicuously under stocked items," although the actual amounts of the antidote stocked were not given. (Skolfield, Lambert *et al.* 1997)
Mixing Protocol *(Optional Reading)*	Protocol for preparing 100 6 mg/3 ml syringes of atropine from bulk powder.

Supplies Needed

Quantity	Description
1	Balance scale
2 g	Atropine sulfate monohydrate powder
1	10 ml sterile water vial
1	10 ml syringe
1	0.2 µ filter (B. Braun PFS 3000)
1	18 gauge needle for transfer
1	1 L normal saline IV solution bag
100	3 ml syringes and needles
1	Syringe batch system (or male-to-male adapter and 60 ml syringes)
100	Syringe labels
not specified	Alcohol swabs
Step	**Procedure using a commercial syringe-batching system**
1	Weigh out 2 g of Atropine sulfate monohydrate powder.
2	Dilute the atropine in 10 ml of sterile water.
3	Remove 50 ml from 1 L bag of normal saline.
4	Instill atropine from (step 2) into 1 L bag of normal saline using 0.2 um filter.
5	Print labels.
6	Connect 1 L bag of diluted atropine (from step 4) to syringe-batching system.
7	Set up (program-calibrate) syringe pump of syringe batching system.
8	Compound and label syringes of atropine solution.
Time required using commercial syringe batching system: 29 min.	
Step	**Manual alternative for last steps of procedure.**
6	Connect 60 ml syringe and fill it from 1 L bag of diluted atropine (from step 4) via male-to-male connecter.
7	With solution in 60 ml syringe, fill 3 ml syringes and label.
Time required using manual batching procedure: 34 min.	
Modified from: Kozak RJ, Siegel S, Kuzma J. Rapid atropine synthesis for the treatment of massive nerve agent exposure. *Annals of Emergency Medicine*. May 2003; 41:685-688.	

Support Available from the CDC Strategic National Stockpile ***(Optional Reading)***	The Centers for Disease Control and Prevention (CDC) maintains the Strategic National Stockpile (SNS), which contains large quantities of medicines and medical supplies that can be used in a public health emergency large enough to deplete local supplies. Once Federal and local authorities agree that the Stockpile is needed, it can be delivered to any state in the U.S. or its territories within 12 hours. Each state is then responsible for receiving and distributing stockpile contents to the local communities that need them. Stockpile contents relevant to cholinesterase inhibitor poisoning include: • 2-PAM. • Atropine. • Diazepam. • Mechanical ventilators are also available (but within 24-36 hours or less). The SNS is also fielding local ChemPacks (each containing medications for 1,000 victims) in each state, which do not require Federal authorization for their release. To find out how to request supplies from ChemPacks or the Strategic National Stockpile, contact your local (or state) emergency management or public health agency.
Key Points	• Stockpiles of antidotes and ventilators are an important aspect of planning for disasters involving cholinesterase inhibitors (*e.g.,* terrorist attacks with nerve agents). • One of these antidotes, atropine, can be rapidly and economically constituted from bulk powder. • Contact your public health or emergency management agency for information on accessing the Strategic National Stockpile.

Syrup of Ipecac, Gastric Lavage, Cathartics, and Activated Charcoal

Learning Objectives

Upon completion of this section, you should be able to

- Describe the roles of the following treatment modalities in the management of poisoning due to cholinesterase inhibitors:
    - Syrup of ipecac.
    - Gastric lavage.
    - Cathartics.
    - Activated charcoal.

Treatments No Longer Recommended as Routine Treatments for Poisoning

Data is lacking to show that any of the following treatments improve the outcome in poisoned patients:

- Activated charcoal.
- Cathartics.
- Gastric lavage.
- Syrup of ipecac.

Furthermore, these treatments can be associated with morbidity. Therefore they are no longer recommended as routine treatments. (American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists 1997)

The presence of vomiting and diarrhea in cholinesterase poisoning would certainly obviate such treatment in any case. Finally, it is contraindicated if the diluent for the cholinesterase inhibitor is a hydrocarbon with high aspiration potential. (Durham and Hayes 1962; American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists 1997; Clark 2002)

While there is no evidence that activated charcoal improves the clinical outcome in poisoning cases, some would consider administrating activated charcoal, if the (American Academy of Clinical Toxicology and European Association of Poison Centres and Clinical Toxicologists 1997)

- Activated charcoal is given *within 1 hour* of the ingestion of a potentially toxic dose.
- Cholinesterase inhibitor is known to be adsorbed by charcoal, **and**
- Patient has an intact or protected airway.

Note: Persistent levels of cholinesterase inhibitors have been detected in the gastric contents of some patients suffering from the intermediate syndrome (a delayed manifestation of cholinesterase inhibitor poisoning --- discussed later). (De Bleecker, Van Den Neucker *et al.* 1993) Although one might conclude that charcoal and gastric emptying might improve outcome for these cases. This has not yet been subjected to empirical study.

Key Points	• Evidence is lacking to demonstrate that syrup of ipecac, activated charcoal, and cathartics improve outcome in poisoning.
Progress Check	43. For which of the following treatments is there good evidence that they improve the outcome in cases of acute cholinesterase inhibitor poisoning? (Choose **ALL** correct answers.) A. Activated charcoal. B. Cathartics. C. Syrup of ipecac or gastric lavage. D. None of the above. *To review relevant content, see "Treatments No Longer Recommended as Routine Treatments for Poisoning" in this section.*

Section 12: Public Health and Medico-Legal Issues

Learning Objectives

Upon completion of this section, you should be able to

- Describe the importance of notifying public health authorities and other emergency response agencies in poisonings due to cholinesterase inhibitors.

Introduction

Healthcare workers are often the first to identify a sentinel patient in what turns out to be a full-blown disease outbreak, (Reigart and Roberts 1999) disaster, or terrorist attack.

Several actions are important to take to reduce morbidity and mortality in cholinesterase poisoning cases.

- Notification of appropriate public health agencies.
- Determination if the patient's history suggests that others may also have been exposed.
- If information suggests the possibility of a multi-casualty or terrorist event, prompt notification of other emergency response agencies in the area (*e.g.,* area hospitals, clinics, urgent care centers, private physician offices, emergency management offices, fire departments, police, EMS providers, hazmat teams and poison centers) so they can have advance notice and be prepared to handle a hazardous materials emergency.

Saving of clothing, body fluids, and belongings in a safe, secured area in case needed for evidence (preserve the chain of evidence). This should be done in a way that also protects against secondary exposure.

Key Points

- Accidents and terrorist attacks involving cholinesterase inhibitors have the potential of affecting multiple victims.
- An important aspect of patient management is to notify public health agencies, and other emergency response agencies (*e.g.,* fire departments, police, EMS providers, hazmat teams, poison centers, and other hospitals, clinics, urgent care centers, and private physician offices) that an exposure has occurred and that they, too, may have to deal with contaminated patients. Community disaster plans should provide a mechanism for accomplishing this task rapidly.
- Isolate and save potential forensic evidence (*e.g.,* clothing, body fluid samples, and belongings).

Progress Check

44. Which of the following area emergency response agencies should be promptly notified in the event of a cholinesterase inhibitor exposure with the potential for multiple victims? (Choose **ALL** correct answers.)

    A. Area EMS providers.
    B. Private physicians' offices.
    C. The local/regional poison center.
    D. The public health agency.
    E. None of the above.

    To review relevant content, see "Introduction" in this section.

Part 5: The Intermediate Syndrome

Learning Objectives

Upon completion of this portion of the case study, the learner should be able to describe the:

- Clinical findings in the intermediate syndrome.
- Significance of the intermediate syndrome in regards to morbidity and mortality due to cholinesterase inhibitor poisoning.
- Treatment and prognosis for intermediate syndrome.

Intermediate Syndrome is a Delayed Onset of Muscle Weakness and Paralysis

The intermediate syndrome is a delayed-onset of muscular weakness and paralysis following an episode of acute cholinesterase inhibitor poisoning. It is so named because it can occur between 24-96 hours (1-4 days) after resolution of the acute cholinergic toxidrome and the onset of organophosphate-induced delayed neuropathy (OPIDN) which has been reported to occur 2-3 weeks after resolution of the acute toxidrome. (Karalliedde and Senanayake 1989; Kwong 2002) (OPIDN is discussed in Part 6.)

Recent studies have shown that intermediate syndrome is accompanied by the excretion of cholinesterase inhibitor metabolites in the urine and by severe depression in cholinesterase levels. It has been suggested that the condition may reflect the recirculation of lipid soluble cholinesterase inhibitors from body fat compartments or gastric fluids. (De Bleecker, Willems *et al.* 1992; De Bleecker, Van Den Neucker *et al.* 1993)

Organophosphorus pesticides

Although acute intoxication with any organophosphorus compound can be followed by the development of the intermediate syndrome, (Jamal 1997) the following have been most often implicated: (Karalliedde, Wheeler *et al.* 2000)

- Diazenon
- Dimethoate
- Fenthion
- Malathion
- Methamidophos
- Methylparathion
- Monocrotophos
- Parathion

Carbamates

Leon *et al.* have reported one case of intermediate syndrome that was attributed to carbamate exposure. (Leon *et al.* 1996)

Nerve agents

The syndrome has not been observed after nerve agent poisoning. (Karalliedde, Wheeler *et al.* 2000)

Incidence

Estimates are that 10-68% of those poisoned with organophosphorus agents will develop intermediate syndrome. (Leon, Pradilla *et al.* 1996; Karalliedde, Wheeler *et al.* 2000)

Although some authors have maintained that the syndrome only occurs after severe cases of acute toxicity, (De Bleecker, Van Den Neucker *et al.* 1993; Ray 1998; Kwong 2002) Khan *et al.* (2001) found that the syndrome occurred in 22% of those with mild poisoning and 17% of those with moderate poisoning. (Khan, Hemalatha *et al.* 2001)

Signs and Symptoms Typically Seen (Karalliedde and Senanayake 1989; Clark 2002; Erdman 2004)

Karalliedde (Karalliedde and Senanayake 1989) first described the syndrome in 1987 and observed that, although clinical findings occurred in a delayed fashion, they were described as acute in onset.

Signs and symptoms that were typically present included:

***Muscle weakness and paralysis of*:**

Muscles enervated by cranial nerves:

Different combinations of muscles enervated by cranial nerves III-VII and X were involved.

Neck flexors:

A constant feature, and one of the earliest signs, was marked weakness of the neck flexors and inability of patients to raise their heads off their pillows.

Proximal limb muscle weakness:

This most typically involved shoulder abductors and hip flexors.

Respiratory muscles:

Patients initially were anxious and restless from hypoxia. Those that could would try to sit up to breath. They were bathed in sweat and using all their accessory respiratory muscles.

Deep tendon reflexes

Deep tendon reflexes were decreased or absent in most patients, although cases of hyperreflexia has sometimes been seen.

Muscle fasciculations

Fasciculations are rare, although spasticity and dystonic reactions were occasionally observed.

	Muscarinic signs Some authors have concluded that muscarinic signs do not occur in patients with the intermediate syndrome (although --- as noted above --- sweating, anxiety, and restlessness, attributed to hypoxia, were noted). However, De Bleecker *et al.* (1993) (De Bleecker, Van Den Neucker *et al.* 1993) observed in a prospective study that 6 out of 8 cases developed short relapses of muscarinic findings that were relieved by increasing the atropine dosage. (De Bleecker, Van Den Neucker *et al.* 1993) ***Loss of sensation*** Loss of sensation was not observed.
Complications	The neuromuscular effects can progress to frank paralysis with respiratory failure and death. Unfortunately, many cases are not diagnosed until significant respiratory insufficiency has developed. (Erdman 2004) Data from India implicates the syndrome as the main cause of morbidity and mortality from organophosphorus poisoning. (Khan, Hemalatha *et al.* 2001)
Treatment	If muscarinic findings occur, they appear to respond to an increase in atropine dose. Although De Bleecker *et al.* (1993) concluded that oxime treatment did not alter the course of the syndrome; the doses used may have been insufficient. It has been suggested that the syndrome may reflect inadequate oxime therapy. In any case, supportive treatment, including mechanical ventilation when needed, is very important. (Kwong 2002)
Disposition	The risk of intermediate syndrome has important implications for patient management, because those who have apparently recovered from the acute cholinergic toxidrome may then suffer from acute respiratory failure or arrest 3-4 days later. Close monitoring and observation during this period is therefore warranted. (Benson, Tolo *et al.* 1992)
Prognosis	If there has not been hypoxic damage, and if proper supportive care has been provided, survival can be expected in most cases. The condition usually resolves spontaneously within 1-2 weeks. (Karalliedde and Senanayake 1989; Erdman 2004)
Key Points	• The intermediate syndrome is a condition of muscular weakness and paralysis that occurs 1-4 days after the resolution of acute cholinergic toxidrome due to organophosphate exposure. • Many cases are not diagnosed until significant respiratory insufficiency has occurred. • It can be a major cause of organophosphate-induced morbidity and mortality. • If hypoxic damage has not occurred, and with proper supportive care, the condition usually resolves spontaneously in 1-2 weeks.

Progress Check

45. Which of the following clinical findings are characteristic of intermediate syndrome? (Choose **ALL** correct answers.)

    A. Fasciculations
    B. Depression or loss of deep tendon reflexes.
    C. Proximal limb muscle weakness.
    D. Distal limb muscle weakness.
    E. Weakness of neck flexors.
    F. Acute respiratory distress.
    G. CNS depression.
    H. Cranial nerve palsies.
    I. Onset 2-3 weeks after resolution of the acute cholinergic toxidrome.
    J. None of the above.

    To review relevant content, see "Signs and Symptoms Typically Seen" in this section.

46. The prognosis for intermediate syndrome is (Choose **ALL** correct answers.)

    A. Poor, regardless of treatment.
    B. Excellent, with supportive care in the absence of hypoxic damage.
    C. None of the above.

    To review relevant content, see "Prognosis" in this part.

Part 6: Organophosphate-Induced Delayed Neuropathy (OPIDN)

Learning Objectives

Upon completion of this section, you should be able to

- Identify the clinical findings in OPIDN compared to the intermediate syndrome.
- Identify the available treatments for OPIDN.
- Describe the current knowledge about the cause of OPIDN.

Introduction

OPIDN, sometimes also called organophosphate induced delayed polyneuropathy (OPIDP) is a rare, delayed neurotoxic effect, which occurs 1-5 weeks after *severe* toxicity from some cholinesterase inhibitors. However, it is not thought to be due to the effects on acetylcholinesterase itself. (Jamal 1997; Clegg and van Gemert 1999; Jokanovic, Stukalov *et al.* 2002; Erdman 2004)

Although it is usually associated with organophosphorus compounds including nerve agents, several cases have been reported that are possibly related to carbamates. (Clark 2002; Abou-Donia 2003)

Etiology

The cause of this condition is unknown. (Jamal 1997) While some have associated this condition with inhibition of an enzyme called neurotarget esterase (NTE), this association more recently has been called into question. (Jamal 1997; Abu-Qare and Abou-Donia 2002; Walker and Nidiry 2002; Abou-Donia 2003)

Pathology

The condition is associated with symmetrical sensory-motor axonal degeneration of the peripheral nerves and spinal cord. (Marrs and Dewhurst 2000; Abu-Qare and Abou-Donia 2002) The lesion, a form of chemical transection known as Wallerian-type degeneration, is followed by myelin degeneration of distal portions of the long and large-diameter tracts of the central and peripheral nervous system. (Abou-Donia 2003)

Signs and Symptoms

Early symptoms

These include sharp, cramp-like pains in the calves. (Jokanovic, Stukalov *et al.* 2002)

Severity

Less severe cases exhibit a characteristic high-stepping gait. (Marrs and Dewhurst 2000) The initial muscle weakness gives rise to a clumsy, shuffling gait. (Ecobichon 1996) The most disabling feature is the paralysis of the legs. In severe cases, quadriplegia with foot and wrist drop are seen, as well as mild pyramidal signs. (Jokanovic, Stukalov *et al.* 2002)

Progression

The neuropathic findings begin peripherally and proceed proximately. Lower extremity paresthesias may appear with a “stocking-glove” distribution and progress to weakness, ataxia, depression of deep tendon reflexes, and paralysis with occasional progression to the arms and

	hands. (Aaron and Howland 1994; Tareg *et al.* 2001; Clark 2002; Jokanovic, Stukalov *et al.* 2002) Pain and weakness spreads rapidly, and patients become unsteady and unable to keep their balance. (Jokanovic, Stukalov *et al.* 2002) This is subsequently replaced by spasticity, hypertonicity, hyperreflexia, clonus, and abnormal reflexes, indicative of damage to the pyramidal tracts and a permanent upper motor neuron syndrome. (Ecobichon 1996)
Treatment	No specific treatment has been identified. (Marrs and Dewhurst 2000) The early administration of pralidoxime and atropine does not seem to prevent the condition. (Tareg *et al.* 2001)
Prognosis	Patients with mild cases recover over several months; those with more serious polyneuropathies have persistent effects. (Clegg and van Gemert 1999; Kwong 2002) Recovery affects only sensory nerves, while motor neurons may permanently lose function. The prognosis for functional recovery depends on the degree of pyramidal involvement, with ataxia and paralysis representing a permanent outcome in severe cases. (Jokanovic, Stukalov *et al.* 2002)
Key Points	• OPIDN is a rare, delayed neurotoxic effect, which occurs 1-5 weeks after severe cholinesterase inhibitor toxicity. • The cause of OPIDN is unknown. • The condition results in weakness, paralysis, pain, and paresthesia. • Sensory recovery occurs, but motor loss can be permanent. • No specific treatment has been identified.
Progress Check	47. In contrast to intermediate syndrome, OPIDN has the following features. (Choose **ALL** correct answers.) A. Pain. B. Paresthesias. C. Longer time until onset. D. Progression of findings from peripherally to proximally. E. Longer duration of clinical abnormalities. F. None of the above. *To review relevant content, see "Signs and Symptoms" in this section.* 48. The cause of OPIDN is: (Choose the **ONE** BEST answer.) A. Inadequate use of 2-PAM in the cholinergic toxidrome. B. Excessive acetylcholine levels. C. Unknown. D. None of the above. *To review relevant content, see "Etiology" in this section.* 49. Effective treatment for OPIDN includes (Choose **ALL** correct

answers.)

A. Neurotarget esterase.
B. 2-PAM
C. Atropine.
D. None of the above.

To review relevant content, see "Treatment" in this section.

Part 7: Organophosphorus Ester-Induced Chronic Neurotoxicity (OPICN)

Learning Objectives

Upon completion of this section, you should be able to describe:

- Our current level of understanding about the association of OPICN and asymptomatic exposures to cholinesterase inhibitors.
- Currently recommended treatment options.

Introduction

Organophosphorus ester-induced chronic neurotoxicity (OPICN) --- also called chronic organophosphate-induced neuropsychiatric disorder (COPIND) --- is a set of long-term, persistent, chronic neuropsychiatric findings that some have attributed to cholinesterase inhibitor toxicity.

Signs and Symptoms

Some of the signs and symptoms that have been ascribed to this condition include (Jamal 1997; Abou-Donia 2003)

Apathy	Decreased visual memory	Impaired vigilance	Reduced abstract reasoning
Anxiety	Depression	Increased social isolation	Reduced fine motor coordination
Confusion	Dizziness	Insomnia	Reduced vibrotactile sensitivity
Decreased academic skills	Emotional lability	Irritability	Short-term memory deficits
Decreased verbal attention	Fatigue	Problems with concentration	Slowing of reaction time

CONTROVERSY: There is a great deal of debate surrounding the subject of Organophosphorus ester-induced chronic neurotoxicity (OPICN). (Jamal 1997; Bateman 1999; Vale 1999; Colosio, Tiramani *et al.* 2003) It has been argued that the condition can follow either an acute, symptomatic exposure or repeated, asymptomatic exposures. (Abou-Donia 2003)

A number of the key studies supporting this argument, particularly those relating to asymptomatic exposures, have been criticized on methodological grounds. (Bateman 1999; Vale 1999; Colosio, Tiramani *et al.* 2003) In particular, determination of exposure in most studies has been based on recall rather than on objective measurements. This method of assessing exposure has not been shown to be very reliable. (Boyer, Templin *et al.* 1995) In addition, a number of the studies have been based on recall of exposures to pesticides in general, rather than specifically to cholinesterase inhibitors.

Some have pointed out that neuropsychiatric findings following severe acute exposures are consistent with damage from seizures and hypoxia, and may not represent a specific toxic effect. (Vale 1999) However, current evidence cannot rule out such a toxic effect, and better-designed studies are needed to resolve the debate. (Colosio, Tiramani *et al.* 2003)

Treatment	No specific treatment has been identified.
Key Points	• Studies suggesting that OPICN result from asymptomatic, chronic exposure to cholinesterase inhibitors have suffered from methodological problems. • Clinical findings attributed to OPICN are consistent with brain damage due to hypoxia and seizures and my not represent a specific toxic effect. • No specific treatment for OPICN has yet been identified.
Progress Check	50. Which of the following is correct about organophosphorus ester-induced chronic neurotoxicity (OPICN) (Choose **ALL** correct answers.) A. It has been established by objective measurement of exposures in humans that this condition occurs with repeated or chronic asymptomatic exposures to cholinesterase inhibitors. B. Is consistent with damage from seizures and hypoxia. C. Is controversial. D. None of the above. *To review relevant content, see "Controversy" in this section.* 51. Effective treatment for OPICN includes (Choose **ALL** correct answers.) A. Neurotarget esterase. B. 2-PAM. C. Atropine. D. None of the above. *To review relevant content, see "Treatment" in this section.*

Part 8: Other Issues Related to Cholinesterase Inhibitor Exposure

Learning Objectives

Upon completion of this section, you should be able to

- Describe the association between cholinesterase inhibitor exposure and
  - Cancer risks.
  - Fetal effects.
  - Gulf War I illness
  - Immune system effects.

Cancer Risks

Generally, *organophosphorus compounds* are not thought to be carcinogenic, although there is some controversy about this. (Poisindex Editorial Staff 2005) Although a number of studies have concluded that *pesticide* exposure increased the risk of some childhood cancers, these studies suffered from significant methodological problems.

These have included:

- Exposure assessments based on parental recall of home exposures (sometimes as far back as 20 years), rather than direct measurement of the actual pesticides.
- Failure of exposure assessments to distinguish between herbicides, insecticides, fungicides, or other types of pesticides, much less cholinesterase inhibitors. (Nurminen 1995; Daniels J 1997; Pagoda and Preston-Martin 1997; Daniels, Olshan *et al.* 2001)
- Potential biases in the selection of controls.
- Retrospective presumption of exposure based on job title and industry where employed.
- Small sample sizes.

Note: One study of Gulf War Veterans exposed to sarin and cyclosarin from the 1991 explosion of the Khamisiyah chemical munitions cache in Iraq found an almost 2-fold increase in subsequent brain cancer deaths. In this study, exposure was assessed using plume modeling and the location of the soldier's company at the time of the explosion. However, the investigators noted that neither sarin nor cyclosarin are known carcinogens, so the cancer deaths could have been due to other chemicals released in the explosion. (Bullman, Mahan *et al.* 2005)

Fetal Effects

Some organophosphorus compounds have been shown to cross the placenta in animals. However, there is a lack of evidence that fetal toxicity has occurred in the absence of maternal toxicity. The few reported cases in humans where pregnant women were poisoned were managed successfully with standard treatment. (Arbuckle and Sever 1998; Erdman 2004)

Currently, there is a lack of convincing evidence that cholinesterase inhibitors cause birth defects or adverse effects on the reproductive system in humans. Although many studies have been carried out, they suffer from serious methodological problems. There are human case reports on third trimester exposures that did not result in birth defects.

	Animal data are conflicting. While some animal studies suggest that birth defects could result from exposure to cholinesterase inhibitors, others do not. Thus, the possibility that birth defects could occur has neither been confirmed nor ruled out. (Minton and Murray 1988; Sever 1997; Shaw, Wasserman *et al.* 1999; Erdman 2004) Experience with oxime treatment of pregnant patients is almost non-existent. Only six cases have been published describing the findings in pregnant victims of organophosphate poisoning. In only 3 cases did these patients receive oxime treatment. One mother, who received obidoxime, elected to have an abortion. The findings in the aborted fetus were not reported. The other two patients were at 16 weeks and 36 weeks of gestation at the time of exposure, and were treated with 2-PAM and atropine. Both delivered normal term infants. (Bailey 1997)
Gulf War I Illness	An extensive review of the literature carried out by the RAND Corporation came to the following conclusions about the association between cholinesterase inhibitors and Gulf War I illness (Cecchine, Golomb *et al.* 2000) • Cholinesterase inhibitors can cause some signs and symptoms similar to those found in Gulf War I illness. • However, based on the evidence available, one cannot explain the myriad health problems reported by Persian Gulf War (I) veterans on the basis of exposure to cholinesterase inhibitors. • The evidence also does not currently allow us to rule out cholinesterase inhibitors as a contributing factor.
Immune System Effects	There are a multitude of physiological processes that lead to effective immune system function, and the immunotoxic disruption of any one of them may not necessarily alter host resistance. Studies in laboratory animals have documented immunotoxic effects of organophosphorus compounds, and in some cases have even linked them with altered disease resistance. However, there is a lack of clear-cut evidence to show that exposure to these compounds alters overall immune function in humans. (Galloway and Handy 2003)
Key Points	• Currently, convincing evidence does not exist to confirm or rule out cancer, birth defects or immune system effects due to exposure to cholinesterase inhibitors. • Current evidence is also lacking to verify or reject a causal relationship between exposure to cholinesterase inhibitors and the development of Gulf War I illness.

Progress Check

52. A causal relationship in humans exists between cholinesterase inhibitor exposure and which of the following: (Choose **ALL** correct answers.)

    A. Birth defects.
    B. Cancer.
    C. Gulf War I illness
    D. None of the above.

    To review relevant content, see "Fetal Effects," "Cancer Risks," and "Gulf War Illness" in this section.

Agency for Toxic Substances and Disease Registry
Case Studies in Environmental Medicine
Cholinesterase Inhibitors: Including Pesticides & Chemical Warfare Nerve Agents

Posttest Instructions

Introduction

ATSDR seeks feedback on this course so we can assess its usefulness and effectiveness. We ask you to complete the assessment questionnaire online for this purpose.

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To complete the assessment and posttest, go to www2.cdc.gov/atsdrce and follow the instructions on that page.

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Posttest

Please select the best correct answer(s)

1. Which of the following community emergency response agencies should be involved in planning for disasters such as those involving mass exposures to cholinesterase inhibitors? (Choose **ALL** correct answers)

   A. Emergency management/disaster offices.
   B. All area hospitals.
   C. The poison center.
   D. Fire departments.
   E. EMS providers.
   F. The Local Emergency Planning Committee (LEPC).
   G. None of the above.

2. Which of the following should be assumed to happen with incidents involving patients acutely exposed to cholinesterase inhibitors (Choose **ALL** correct answers)

   A. Patients will be transported to the hospital without having been decontaminated.
   B. Chemically exposed patients will be sent to a single hospital in the community designated for chemical casualties.
   C. Contaminated patients will arrive unannounced.
   D. None of the above.

3. Cholinesterase inhibitor toxicity leads to (Choose **ALL** correct answers)

   A. Excessive cholinesterase activity.
   B. Depression of cholinesterase activity.
   C. Excessive amounts of acetylcholine.
   D. Occupation of cholinesterase binding sites by the cholinesterase inhibitor.
   E. None of the above.

4. Which of the following are among the 4 major types of pathology caused by cholinesterase inhibitors? (Choose **ALL** correct answers)

   A. The cholinergic toxidrome.
   B. The acute polyneuropathic syndrome.
   C. The intermediate syndrome.
   D. Organophosphate-induced delayed neuropathy.
   E. None of the above.

5. The key function of nicotinic receptors is to (Choose **ALL** correct answers)

   A. Trigger excretion of exocrine glands.
   B. Trigger rapid neural and neuromuscular transmission.
   C. Suppress rapid neural and neuromuscular transmission.
   D. Modulate intrinsic rhythmic electrical and mechanical activity.
   E. None of the above.

6. Which of the following effects of acute cholinesterase toxicity involve nicotinic receptors? (Choose **ALL** correct answers)

   A. Sweating.
   B. Miosis (pupillary constriction).
   C. Hyperglycemia.
   D. Fasciculations.
   E. None of the above.

7. In which of the following anatomical locations are nicotinic receptors found? (Choose **ALL** correct answers)

   A. Neuromuscular junctions.
   B. Sympathetic nervous system.
   C. Autonomic ganglia.
   D. Central nervous system.
   E. None of the above.

8. Muscarinic receptors (Choose **ALL** correct answers)

   A. Are faster to respond than nicotinic receptors.
   B. Are not found in the central nervous system.
   C. Trigger bronchodilation.
   D. Trigger mostly sympathetic nervous system effects.
   E. None of the above.

9. Which of the following are true about the cholinergic toxidrome? (Choose **ALL** correct answers)

   A. CNS effects are mediated by both nicotinic and muscarinic receptors.
   B. CNS effects can mimic mental illness.
   C. Uncontrolled seizures can lead to long-term CNS effects.
   D. Seizures are more common in adults than children.
   E. None of the above.

10. Acute cholinesterase inhibitor toxicity has been known to result in the following laboratory abnormalities (Choose **ALL** correct answers)

    A. Leukocytosis.
    B. Peaked T-waves on EKG.
    C. Elevated serum glucose.
    D. Hyperkalemia or hypokalemia.
    E. None of the above.

11. Which of the following medical conditions can be mimicked by cholinesterase inhibitor toxicity? (Choose **ALL** correct answers)

    A. Mental illness.
    B. Food poisoning.
    C. Opiate overdose.
    D. Influenza.
    E. None of the above.

12. Pediatric cholinesterase inhibitor poisoning differs from that in adults in the following ways (Choose **ALL** correct answers)

    A. Seizures are less likely.
    B. Nicotinic effects are more likely.
    C. Fasciculations are more common.
    D. Bradycardia is less common.
    E. None of the above.

13. Potential sources of exposure to cholinesterase inhibitors include which of the following (Choose **ALL** correct answers)

    A. Insecticides.
    B. Antiparkinson drugs.
    C. Snake venom.
    D. Malaysian Bean sprouts.
    E. None of the above.

14. Which of the following questions should be included in history for suspected cholinesterase inhibitor exposure? (Choose **ALL** correct answers)

    A. Typical work activities.
    B. Medications.
    C. Hobbies.
    D. Use of traditional or ethnic remedies.
    E. None of the above.

15. Which of the following are true about laboratory tests for cholinesterase inhibitor toxicity? (Choose **ALL** correct answers)

    A. The rapid availability of RBC cholinesterase levels, compared to serum cholinesterase levels makes them a useful tool for the emergency management of acutely toxic patients.
    B. Reduction in RBC cholinesterase levels to normal is a good end point for titration for initial doses of 2-PAM.
    C. Normal ranges of serum cholinesterase vary widely among individuals, but RBC cholinesterase level normals vary little among individuals.
    D. Since the imposition of federal laboratory standards, the normal ranges for serum and RBC cholinesterase levels are the same for each laboratory.
    E. None of the above.

16. Supportive care is an important aspect of treatment for the cholinergic toxidrome and should be focused primarily on maintaining and improving (Choose the **ONE BEST** answer)

    A. Renal function.
    B. Hepatic function.
    C. Respiratory function.
    D. CNS function.
    E. None of the above.

17. Atropine counteracts cholinesterase inhibitor toxicity by (Choose the **ONE BEST** answer)

    A. Competitively occupying muscarinic receptor sites.
    B. Competitively occupying nicotinic receptor sites.
    C. Competitively occupying nicotinic and muscarinic receptor sites.
    D. Neutralizing acetylcholine.
    E. None of the above.

18. Which of the following is/are the best end-points against which to titrate the dose of atropine in acute cholinesterase poisoning? (Choose the **ONE BEST** answer)

    A. Pupillary dilation.
    B. Pupillary constriction.
    C. Clinically significant reduction of bronchorrhea and bronchoconstriction, (as reflected by level of oxygenation and ease of ventilation).
    D. Development of heart rate of between 100-150/min.
    E. Return of consciousness.
    F. Return of muscle strength.
    G. all of the above.
    H. None of the above.

19. In order of preference, the best routes of atropine administration are: (Choose the **ONE BEST** answer)

    A. Intramuscular is better than Intravenous which is better than Autoinjector.
    B. Intravenous is better than Autoinjector which is better than Intramuscular.
    C. Autoinjector is better than Intravenous which is better than Intramuscular.
    D. Intravenous is better than Intramuscular which is better than Autoinjector.
    E. Intravenous is best; Intramuscular and Autoinjector are equally good.
    F. None of the above.

20. Which type of cholinesterase toxicity can require the highest doses of atropine? (Choose the **ONE BEST** answer)

    A. Inhalation of nerve agent.
    B. Dermal exposure to organophosphorus agents.
    C. Suicidal ingestion of organophosphorus agents.
    D. Ingestion of carbamates.

21. Which of the following are true about 2-PAM? (Choose **ALL** correct answers)

    A. It should not be used in carbamate poisoning.
    B. It works by attaching to the cholinesterase inhibitor bound to cholinesterase, attaching to and removing the inhibitor.
    C. It reduces the effectiveness of atropine.
    D. It is ineffective after aging occurs.
    E. None of the above.

22. Which of the following are reasons for treatment failure with 2-PAM? (Choose **ALL** correct answers)

    A. Inadequate dose.
    B. Co-administration of atropine.
    C. Redistribution of cholinesterase inhibitor from fat tissue.
    D. Aging has already occurred.
    E. None of the above.

23. Which of the following lead to delayed aging, and therefore prolongation of the time course when 2-PAM is still effective? (Choose **ALL** correct answers)

    A. Co-administration of atropine.
    B. Poisoning from fat-soluble organophosphorus compounds.
    C. Dermal exposure.
    D. Poisoning with chemicals that must be metabolically converted before they possess cholinesterase inhibiting properties.
    E. None of the above.

24. Which of the following is true about seizures resulting from cholinesterase inhibitors? (Choose **ALL** correct answers)

    A. They are more common in adults than in children.
    B. Although diazepam is effective in controlling seizures, it has not been shown to improve clinical outcome.
    C. Diazepam should not be used unless seizures occur.
    D. CNS damage from cholinesterase inhibitors is due to a direct toxic effect, not seizure activity.
    E. None of the above.

25. Which of the following are currently recommended in the routine treatment of poisoning?

    A. Syrup of ipecac.
    B. Gastric lavage.
    C. Cathartics.
    D. Activated charcoal.
    E. None of the above.

26. Which of the following is true regarding the intermediate syndrome? (Choose **ALL** correct answers)

    A. It most commonly occurs after nerve agent poisoning.
    B. If good supportive care has been given and there is no hypoxic damage, the condition usually resolves spontaneously.
    C. Atropine is indicated if muscarinic signs are present.
    D. Delayed, but sudden-onset of respiratory weakness or paralysis may occur, leading to respiratory failure.
    E. None of the above.

27. Which of the following are true about Organophosphate-induced delayed neuropathy (OPIDN)? (Choose **ALL** correct answers)

    A. It is caused by a molecular alteration of nicotinic receptors at the neuromuscular junction of distal skeletal muscle groups.
    B. Pain is not a characteristic symptom.
    C. If there has not been any hypoxic damage, and good supportive care has been given, full recovery is the rule.
    D. Early and adequate doses of 2-PAM and atropine have been shown to prevent this condition.
    E. None of the above.

28. Which of the following are true about Organophosphorus ester-induced neurotoxity (OPICN) (Choose **ALL** correct answers)

    A. It is a set of long-term, persistent neuropsychiatric signs and symptoms.
    B. No specific treatment has been identified.
    C. Studies carried out to assess whether the condition can occur after asymptomatic exposures to cholinesterase inhibitors have suffered from methodological problems.
    D. It occurs when cholinesterase inhibitors trigger a permanent defect in neurotarget esterase.
    E. None of the above.

29. Which of the following are true about cholinesterase inhibitors? (Choose **ALL** correct answers)

    A. Chronic, asymptomatic exposure to cholinesterase inhibitors is associated with an increased risk of chronic lymphocytic leukemia.
    B. Neural tube defects have been associated with symptomatic exposures during the first trimester of pregnancy.
    C. The available evidence does not explain the myriad of symptoms of Gulf War Illness on the basis of exposure to cholinesterase inhibitors.
    D. The Wenger-Herzold study demonstrated clinically significant long-term decrements in immunity in those with long-term exposure to organophosphorus compounds, but not carbamates.
    E. None of the above.

30. The most characteristic early finding in intermediate syndrome is: (Choose the **ONE BEST**answer)

    A. Loss of sensation in distal extremities.
    B. Inability of the patient to lift his head off the pillow.
    C. Muscle fasciculations.
    D. Profound salivation (liters per day).
    E. None of the above.

31. Muscarinic receptors are found in: (Choose **ALL** correct answers)

    A. Skeletal muscle.
    B. Smooth muscle.
    C. Exocrine glands.
    D. Sweat glands.
    E. None of the above.

32. Which of the following are true about the central nervous system effects of cholinesterase inhibitors (Choose the **ONE BEST** answer)

    A. The pathology can be explained on the basis of increased muscarinic, as opposed to nicotinic, receptor activity.
    B. The pathology can be explained on the basis of increased nicotinic, as opposed to muscarinic, receptor activity.
    C. The pathology is poorly understood but involves both nicotinic and muscarinic receptors.
    D. None of the above.

33. Which of the following central nervous system signs and symptoms have been reported in cases of cholinesterase inhibitor poisoning? (Choose **ALL** correct answers)

    A. Anxiety.
    B. Emotional lability.
    C. Convulsions.
    D. Excess dreaming.
    E. None of the above.

34. Which of the following questions on an exposure history are appropriate for the physician to ask in a patient suffering from signs and symptoms suggestive of cholinesterase inhibitor poisoning? Choose **ALL** correct answers

    A. What are your hobbies?
    B. Do you cook with wild mushrooms?
    C. Does anyone at home have similar signs or symptoms?
    D. Do you handle venomous snakes?
    E. None of the above.

35. Cholinesterase inhibitors block the ability of acetylcholinesterase to break down acetylcholine by? (choose the **ONE** best answer)

    A. Occupying the binding site on cholinesterase to which the acetylcholine would attach.
    B. Preventing the release of acetylcholine from its attachment on cholinesterase.
    C. Attaching to acetylcholine which prevents its attachment to cholinesterase.
    D. None of the above.

36. What causes the cholinergic toxidrome? (Choose the **ONE** best answer)

    A. An excess of acetylcholine.
    B. A deficiency of acetylcholine.
    C. An excess of acetylcholinesterase.
    D. None of the above.

37. Where are cholinergic receptors are found? (Choose **ALL** correct answers)

    A. At the neuromuscular junction.
    B. In the central nervous system.
    C. In the sympathetic, peripheral nervous system.
    D. In the parasympathetic, peripheral nervous system.
    E. None of the above.

38. Nicotinic and muscarinic receptors differ in which the following ways (Choose **ALL** correct answers)

    A. They have different functions.
    B. They have different mechanism by which they trigger signal transmission.
    C. They may exist at different anatomical locations.
    D. None of the above.

39. Why do excessive levels of acetylcholine ("The cholinergic toxidrome") cause different signs and symptoms, depending on whether the nicotinic or muscarinic receptors are involved? (Choose **ALL** correct answers)

    A. Because some nicotinic and muscarinic receptors are located in and affect different anatomic structures.
    B. Because nicotinic and muscarinic receptors are triggered by different neurotransmitters.
    C. Because nicotinic and muscarinic receptors have different mechanisms of action.
    D. None of the above.

40. Factors that account for variation in the clinical presentation of cholinesterase toxicity include: (Choose **ALL** correct answers)

    A. Route of exposure.
    B. The balance of nicotinic and muscarinic effects on the sympathetic and parasympathetic nervous system.
    C. Age of the patient.
    D. The specific cholinesterase-inhibiting chemical.
    E. None of the above.

41. Which of the following are major factors leading to respiratory failure in cases of cholinesterase inhibitor poisoning? (Choose **ALL** correct answers)

    A. Bronchodilation.
    B. Central respiratory depression.
    C. Weakness or paralysis of the respiratory muscles.
    D. Excessive respiratory tract secretions.
    E. None of the above.

42. Which of the following statements are true regarding serum or red blood cell cholinesterase levels? (Choose **ALL** correct answers)

    A. The use of these tests helps to avoid serious errors in emergency treatment.
    B. With current technology, interindividual variation in results, is no longer a significant problem.
    C. While percentage of inhibition in the same person may be different in different laboratories, the absolute cholinesterase values are usually the same.
    D. None of the above.

43. Which of the following statements are true about the laboratory measurement of cholinesterase inhibitors themselves or their metabolites? (Choose **ALL** correct answers)

    A. Each test can measure only one chemical, so it is only useful if you know the specific chemical to which the patient was exposed.
    B. The results are not usually available in time to guide emergency treatment.
    C. The test results are usually very accurate.
    D. None of the above.

44. Which of the following statements is true about the patient with skin exposure to cholinesterase inhibitors? (Choose **ALL** correct answers)

    A. If the patient has only been exposed to cholinesterase inhibitor vapor, there is no risk of secondary exposure.
    B. If the patient has ingested a cholinesterase inhibitor, others can be exposed if the patient vomits.
    C. More important than which decontamination fluid is used is how rapidly decontamination is initiated.
    D. Water and soapy water are very effective decontamination fluids.
    E. None of the above.

45. If a hospital receives a patient with cholinesterase inhibitor toxicity and there is the potential that others were also exposed at the scene, which of the following should be notified (Choose **ALL** correct answers)

    A. All other area hospitals.
    B. The local fire department.
    C. The poison center.
    D. Area EMS providers.
    E. None of the above.

Question	Location of Relevant Content
1.	Community preparedness
2.	Community preparedness
3.	What type of pathology do cholinesterase inhibitors cause?
4.	What type of pathology do cholinesterase inhibitors cause?
5.	Nicotine acetylcholine receptors
6.	Nicotine acetylcholine receptors
7.	Nicotine acetylcholine receptors
8.	Muscarinic acetylcholine receptors
9.	What is the cholinergic toxidrome?
10.	Effects on routine laboratory tests
11.	Differential diagnosis
12.	Signs and symptoms: differences in pediatric cases
13.	Who is at risk for exposure? The exposure history
14.	Who is at risk for exposure? The exposure history
15.	Effects on routine laboratory tests
16.	Management strategy 2: Supportive care
17.	Management strategy 3: Medications - Atropine
18.	Management strategy 3: Medications
19.	Management strategy 3: Medications
20.	Management strategy 3: Medications
21.	Management strategy 3: Medications – 2-PAM
22.	Management strategy 3: Medications

23.	Management strategy 3: Medications
24.	Management strategy 3: Medications - Diazepam
25.	Syrup of ipecac, gastric lavage, cathartics, and activated charcoal
26.	The intermediate syndrome
27.	Organophosphate-induced delayed neuropathy(OPIDN)
28.	Organophosphorus ester-induced chronic neurotoxicity (OPICN)
29.	Other issues related to cholinesterase inhibitor toxicity
30.	The intermediate syndrome
31.	Muscarinic acetylcholine receptors
32.	Clinical findings are due to a mixture of nicotinic and muscarinic effects
33.	Clinical findings are due to a mixture of nicotinic and muscarinic effects
34.	Who is at risk for exposure? The exposure history
35.	What are cholinesterase inhibitors?
36.	The cholinergic toxidrome: What is the cholinergic toxidrome?
37.	The cholinergic toxidrome: What is the cholinergic toxidrome?
38.	The cholinergic toxidrome: What is the cholinergic toxidrome?
39.	The cholinergic toxidrome: What is the cholinergic toxidrome?
40.	The cholinergic toxidrome: Clinical findings in cholinesterase inhibitor toxicity are due to a mixture of nicotinic and muscarinic effects. The cholinergic toxidrome: Signs and Symptoms: differences in pediatric cases
41.	Management strategy 2: supportive care
42.	Laboratory Assessment of the Cholinergic Toxidrome: Red Blood Cell (RBC) and Serum Cholinesterase Levels
43.	Laboratory Assessment of the Cholinergic Toxidrome: Direct Measurement of Cholinesterase Inhibitors and Their Metabolic Byproducts
44.	Management of the Cholinergic Toxidrome: Management Strategy 1: Prevention of Secondary Exposure
45.	Public Health and Medico-Legal Issues

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Answers to Progress Check Questions

1. Which of the following community emergency response agencies should be involved in planning for disasters such as those involving mass exposures to cholinesterase inhibitors? (Choose **ALL** correct answers.)

   A. All area hospitals. Correct: There is/are (an) other correct answer(s).
   B. Public health agencies. Correct: There is/are (an) other correct answer(s).
   C. The poison center. Correct: There is/are (an) other correct answer(s).
   D. The Local Emergency Planning Committee (LEPC). Correct: There is/are (an) other correct answer(s).
   E. None of the above. Incorrect.

2. Which of the following assumptions form the basis of effective planning for the medical management of patients exposed to and/or contaminated with cholinesterase inhibitors: (Choose **ALL** correct answers.)

   A. Patients will be decontaminated in the field prior to ambulance transport. Incorrect: Many patients are not decontaminated prior to being taken to hospitals. In fact, many will arrive by private vehicle, rather than by ambulance. Therefore, hospitals must be prepared to deal with the arrival of contaminated patients.
   B. Each community should designate a single hospital to receive contaminated casualties. Incorrect: Since it is often the patients who determine hospitals destination, all hospitals should be prepared to deal with them. Designation of a "decontamination hospital" merely creates a false sense of security for the other hospitals, who believe they do not need to prepare for contaminated patients.
   C. Ambulances will give advance notice to hospitals about the arrival of contaminated patients. Incorrect: Since many patients are transported by non-ambulance vehicles, they often arrive at hospitals without advanced notice.
   D. None of the above. Correct.

3. Cholinesterase inhibitor toxicity is due to: (Choose **ALL** correct answers.)

   A. Excessive levels of the enzyme, acetylcholinesterase. Incorrect: Cholinesterase inhibitor toxicity is not due to excessive levels of the enzyme, acetylcholinesterase. Rather, it is due to excessive levels of acetylcholine (sometimes referred to as a "cholinergic crisis").
   B. Depressed activity of the enzyme, acetylcholinesterase. Correct: Cholinesterase inhibitors attach to acetylcholinesterase and deactivate it. There is/are (an) other correct answer(s).
   C. Excessive levels of the neurotransmitter, acetylcholine. Correct: Cholinesterase inhibitor toxicity is due to excessive levels of the neurotransmitter acetylcholine (Note that this is due to inhibition of the enzyme acetylcholinesterase). There is/are (an) other correct answer(s).
   D. Depressed levels of the neurotransmitter, acetylcholine. Incorrect: Cholinesterase inhibitor toxicity is not due to depressed levels of the neurotransmitter, acetylcholine. Rather, it is due to excessive levels of acetylcholine (sometimes referred to as a "cholinergic crisis").
   E. None of the above. Incorrect.

4. Which of the following are true about organophosphorus compounds? (Choose **ALL** correct answers.)

   A. They include pesticides. Correct: There is/are (an) other correct answer(s).
   B. They include nerve agents. Correct: There is/are (an) other correct answer(s).
   C. They are less toxic than carbamates. Incorrect: Carbamates are less toxic than organophosphorus compounds.
   D. They have a longer duration of action than carbamates. Correct: There is/are (an) other correct answer(s).
   E. None of the above. Incorrect.

5. Cholinesterase inhibitors block the ability of acetylcholinesterase to break down acetylcholine by? (Choose the **ONE** best answer)

   A. Occupying the binding site on cholinesterase to which the acetylcholine would attach. Correct: When this site is occupied by the cholinesterase inhibitor, acetylcholine can no longer attach to the site and be broken down. Thus, acetylcholine levels build up to toxic levels.
   B. Preventing the release of acetylcholine from its attachment on cholinesterase. Incorrect: The correct answer is A.
   C. Attaching to acetylcholine, which prevents its attachment to cholinesterase. Incorrect: The correct answer is A.
   D. None of the above. Incorrect: The correct answer is A.

6. Which condition(s) consist of neuropathy characteristically occurring 1-5 weeks after recovery from the acute cholinergic toxidrome (Choose **ALL** correct answers.)

   A. Cholinergic toxidrome. Incorrect. Cholinergic toxidrome is not a condition consisting of a neuropathy, although neuropathic conditions can follow it.
   B. Intermediate syndrome. Incorrect. Intermediate syndrome consists of neuromuscular dysfunction that occurs 24-96 hours after a significant, and usually severe episode of the cholinergic toxidrome
   C. Organophosphate-induced delayed neuropathy (OPIDN). Correct.
   D. Organophosphorus ester-induced chronic neurotoxicity (OPICN). Incorrect. OPICN is a chronic neurodysfunction that lasts for weeks to years after acute exposure, but may not occur in the 1-5 week period after recovery from the acute cholinergic toxidrome.
   E. None of the above. Incorrect.

7. Which condition(s) result(s) in chronic neurological effects that characteristically persist for years? (Choose **ALL** correct answers.)

   A. Cholinergic toxidrome. Incorrect. The cholinergic toxidrome refers to acute toxicity from cholinesterase inhibitor poisoning.
   B. Intermediate syndrome. Incorrect. Usually, the intermediate syndrome resolves spontaneously within 1-2 weeks.
   C. Organophosphate-induced delayed neuropathy (OPIDN). Correct.
   D. Organophosphorus ester-induced chronic neurotoxicity (OPICN). Correct.
   E. None of the above. Incorrect.

8. Nicotinic and muscarinic receptors: (Choose **ALL** correct answers.)

    A. Are both acetylcholine receptors. Correct: Nicotinic and muscarinic receptors are both acetylcholine receptors. There is/are (an) other correct answer(s).
    B. Have the same structure. Incorrect: The correct answers are A, C, and D. (Note that nicotinic and muscarinic receptors are both acetylcholine receptors but have different chemical structures, different physiology, and different functions.)
    C. Have different physiology. Correct: Nicotinic and muscarinic receptors have different physiology. There is/are (an) other correct answer(s).
    D. Have different functions. Correct: Nicotinic and muscarinic receptors have different functions. There is/are (an) other correct answer(s).
    E. None of the above. Incorrect: The correct answers are A, C, and D. (Note that nicotinic and muscarinic receptors are both acetylcholine receptors but have different chemical structures, different physiology, and different functions.)

9. What causes the cholinergic toxidrome? (Choose **ALL** correct answers.)

    A. Elevated levels of acetylcholinesterase. Incorrect: The cholinergic toxidrome refers to toxic symptoms caused by elevated levels of acetylcholine.
    B. Elevated levels of acetylcholine. Correct: Cholinesterase inhibitors block the normal breakdown of acetylcholine, and can lead to markedly elevated levels of acetylcholine, a condition referred to as the cholinergic toxidrome.
    C. Acetylcholine deficiency. Incorrect: The cholinergic toxidrome refers to toxic symptoms caused by elevated levels of acetylcholine.
    D. None of the above. Incorrect: The cholinergic toxidrome refers to toxic symptoms caused by elevated levels of acetylcholine.

10. Cholinergic receptors are found in which of the following locations? (Choose **ALL** correct answers.)

    A. The central nervous system. Correct: There is/are (an) other correct answer(s).
    B. The sympathetic nervous system. Correct: There is/are (an) other correct answer(s).
    C. The parasympathetic nervous system. Correct: There is/are (an) other correct answer(s).
    D. The skeletal neuromuscular junctions. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect: The correct answers are A, B, C, and D.

11. Why do excessive levels of acetylcholine (“The cholinergic toxidrome”) cause different signs and symptoms, depending on whether the nicotinic or muscarinic receptors are involved? (Choose **ALL** correct answers.)

    A. Because some nicotinic and muscarinic receptors are located in and affect different anatomic structures. Correct: There is/are (an) other correct answer(s).
    B. Because nicotinic and muscarinic receptors are triggered by different neurotransmitters. Incorrect: They are both triggered by acetylcholine.
    C. Because nicotinic and muscarinic receptors have different mechanisms of action. Correct: There is/are (an) other correct answer(s).
    D. None of the above. Incorrect.

12. Nicotinic receptors: (Choose **ALL** correct answers.)

    A. Trigger rapid neural transmission. Correct: There is/are (an) other correct answer(s).
    B. Trigger rapid neuromuscular transmission. Correct: There is/are (an) other correct answer(s).
    C. Become stimulated then paralyzed by toxic levels of acetylcholine. transmission Correct: There are other correct answers
    D. Are found only in the autonomic nervous system. Incorrect: Nicotinic receptors are found in the autonomic (sympathetic and parasympathetic), somatic (neuromuscular junctions), and central nervous systems.
    E. None of the above. Incorrect.

13. Over stimulation of nicotinic receptors can cause: (Choose **ALL** correct answers.)

    A. Tachycardia. Correct: There is/are (an) other correct answer(s).
    B. Fasciculations. Correct: There is/are (an) other correct answer(s).
    C. Mydriasis (pupillary dilation). Correct: There is/are (an) other correct answer(s).
    D. Leukopenia. Incorrect: On the contrary, over-stimulation of nicotinic receptors can cause leukocytosis.
    E. None of the above.

14. Nicotinic receptors are found in which of the following locations: (Choose **ONE** best answer)

    A. Sympathetic nervous system. Incorrect: Nicotinic receptors are found in the sympathetic, parasympathetic, and central nervous systems.
    B. Parasympathetic nervous system. Incorrect: Nicotinic receptors are found in the sympathetic, parasympathetic, and central nervous systems.
    C. Central nervous system. Incorrect: Nicotinic receptors are found in the sympathetic, parasympathetic, and central nervous systems.
    D. All of the above. Correct: Nicotinic receptors are found in the sympathetic, parasympathetic, and central nervous systems.
    E. None of the above. Incorrect: Nicotinic receptors are found in the sympathetic, parasympathetic, and central nervous systems.

15. When compared with the action of nicotinic receptors, muscarinic receptors: (Choose **ALL** correct answers.)

    A. Are faster. Incorrect: Muscarinic receptors respond slower than nicotinic receptors.
    B. Initiate rather than modulate smooth muscle activity. Correct: There is/are other correct answer(s).
    C. Have primarily parasympathetic effects on the peripheral nervous system. Correct: There is/are other correct answer(s).
    D. Stimulate sweating via the sympathetic nervous system. Correct: There is/are other correct answer(s).
    E. None of the above. Incorrect.

16. Cholinesterase inhibitor toxicity leads to the following clinical findings mediated by muscarinic receptors: (Choose **ALL** correct answers.)

    A. Miosis (pupillary constriction). Correct: There is/are (an) other correct answer(s).
    B. Bronchorrhea. Correct: There is/are (an) other correct answer(s).
    C. Nausea. Correct: There is/are (an) other correct answer(s).
    D. Bronchospasm. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

17. Muscarinic receptors are found in: (Choose **ALL** correct answers.)

    A. Skeletal muscle. Incorrect: Nicotinic, not muscarinic, receptors are found in skeletal muscle (at the neuromuscular junctions).
    B. Smooth muscle. Correct: There is/are (an) other correct answer(s).
    C. Exocrine glands. Correct: There is/are (an) other correct answer(s).
    D. Sweat glands. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect: Nicotinic, not muscarinic, receptors are found in skeletal muscle (at the neuromuscular junctions).

18. Signs and symptoms of cholinesterase inhibitor poisoning: (Choose **ALL** correct answers.)

    A. May vary depending on the specific chemical involved. Correct: There is/are (an) other correct answer(s).
    B. Are dominated by nicotinic findings in pediatric cases. Correct: There is/are (an) other correct answer(s).
    C. Involving the CNS are primarily due to the presence of muscarinic receptors. Incorrect: They are due to a mixture of muscarinic and nicotinic receptors.
    D. May mimic mental illness. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

19. Death from cholinesterase inhibitor poisoning is usually due to: (Choose the **ONE BEST** answer.)

    A. Cardiac failure. Incorrect: The correct answer is B. Death is usually due to respiratory failure from a combination of central respiratory depression, paralysis of respiratory muscles, bronchoconstriction, and bronchorrhea.
    B. Respiratory failure. Correct: Death is usually due to respiratory failure from a combination of central respiratory depression, paralysis of respiratory muscles, bronchoconstriction, and bronchorrhea.
    C. Renal failure. Incorrect: Death is usually due to respiratory failure from a combination of central respiratory depression, paralysis of respiratory muscles, bronchoconstriction, and bronchorrhea.
    D. Hepatic failure. Incorrect. Death is usually due to respiratory failure from a combination of central respiratory depression, paralysis of respiratory muscles, bronchoconstriction, and bronchorrhea.
    E. None of the above. Incorrect.

20. Which of the following are true about the central nervous system effects of cholinesterase inhibitors: (Choose the **ONE BEST** answer.)

    A. The pathology can be explained based on increased muscarinic, as opposed to nicotinic, receptor activity. Incorrect.
    B. The pathology can be explained based on increased nicotinic, as opposed to muscarinic, receptor activity. Incorrect.
    C. The pathology is poorly understood but involves both nicotinic and muscarinic receptors. Correct.
    D. None of the above. Incorrect.

21. Which of the following central nervous system signs and symptoms have been reported in cases of cholinesterase inhibitor poisoning? (Choose **ALL** correct answers.)

    A. Anxiety. Correct: There is/are (an) other correct answer(s).
    B. Emotional lability. Correct: There is/are (an) other correct answer(s).
    C. Convulsions. Correct: There is/are (an) other correct answer(s).
    D. Excess dreaming. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

22. Cholinesterase toxicity has been known to cause abnormally high levels of which of the following laboratory tests. (Choose **ALL** correct answers.)

    A. Serum glucose. Correct: There is/are (an) other correct answer(s).
    B. White blood cell count. Correct: There is/are (an) other correct answer(s).
    C. Serum amylase. Correct: There is/are (an) other correct answer(s).
    D. CPK. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

23. Cholinesterase inhibitor toxicity can be mistaken for a number of other illnesses. Which of the following indicate that the condition is not due to cholinesterase toxicity? (Choose **ALL** correct answers.)

    A. Presence of fever. Incorrect: Fever occurs in about 25% of cases.
    B. Lack of urinary incontinence. Incorrect: Although it is listed as one of the classic signs of cholinesterase inhibitor toxicity, it is, in fact, absent in over 80% of the cases.
    C. Solvent-like breath odor. Incorrect: Liquid formulations often use hydrocarbon solvents. Their ingestion would be expected to result in a solvent-like breath odor.
    D. Leukocytosis with a left shift. Incorrect: Leukocytosis with a left shift has been reported in numerous cases of cholinesterase inhibitor toxicity.
    E. None of the above. Correct.

24. The cholinergic toxidrome <u>in children</u> is dominated by which type of signs and symptoms? (Choose the **ONE BEST** answer.)

    A. Muscarinic. Incorrect. The cholinergic toxidrome in children is dominated by nicotinic signs and symptoms.
    B. Nicotinic. Correct.
    C. None of the above. Incorrect.
    D. A and B. Incorrect.

25. In the cholinergic toxidrome from cholinesterase inhibitors, seizures are (Choose **ALL** correct answers.)

    A. More common in adults. Incorrect. Seizures are more common in children.
    B. More common in children. Correct.
    C. About equally common in children and adults. Incorrect. Seizures are more common in children.
    D. Very rare in both adults and children. Incorrect. Seizures are more common in children.
    E. None of the above. Incorrect.

26. True or False: Neuromuscular weakness in a small child is easy to overlook unless muscle tone is specifically assessed.

    A. True.

27. Potential sources of exposure to cholinesterase inhibitors include which of the following: (Choose **ALL** correct answers.)

    A. Pesticides. Correct: There is/are (an) other correct answer(s).
    B. Pyridostigmine. Correct: There is/are (an) other correct answer(s).
    C. Castor beans. Incorrect: You were probably thinking of *calabar* beans. The toxic agent in castor beans is ricin, not cholinesterase inhibiting chemicals.
    D. Potato sprouts. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

28. Which of the following questions on an exposure history are appropriate for the physician to ask in a patient suffering from signs and symptoms suggestive of cholinesterase inhibitor poisoning:

    A. What are your hobbies? Correct: There is/are (an) other correct answer(s).
    B. What kind of work do you do? Correct: There is/are (an) other correct answer(s).
    C. Does anyone at home have similar signs or symptoms? Correct: There is/are (an) other correct answer(s).
    D. Do you handle venomous snakes? Correct: Certain snake venoms have cholinesterase inhibiting properties. There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

29. Which of the following statements are true regarding laboratory measurement of cholinesterase inhibitors? (Choose **ALL** correct answers.)

    A. Cholinesterase levels are of key importance to the initial emergency assessment. Incorrect: Cholinesterase levels are rarely available in time to guide emergency treatment, which must be based on clinical assessment.
    B. Failure to refrigerate blood or serum samples tends to cause a falsely low measurement of cholinesterase level. Incorrect: They tend to cause a falsely high level because spontaneous reactivation of cholinesterase may occur.
    C. With cholinesterase inhibitor toxicity, serum levels of cholinesterase become depressed earlier than RBC levels of cholinesterase. Correct: There is/are (an) other correct answer(s).
    D. Serum tests for cholinesterase are more widely available than those for RBC cholinesterase. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

30. Which of the following are true about direct laboratory measurement of cholinesterase inhibitors and their byproducts: (Choose **ALL** correct answers.)

    A. Unlike cholinesterase measurements, they are rapidly available to most hospital emergency departments. Incorrect: They are not usually available in time to guide emergency treatment.
    B. They are only useful, if you know what chemical you are looking for. Correct: Each test analyzes for the presence of only one chemical. There is/are (an) other correct answer(s).
    C. Toxic levels for individual agents have not been established. Correct: There is/are (an) other correct answer(s).
    D. They may be useful for forensic documentation of exposure. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

31. Strategies helpful in reducing secondary exposure include: (Choose **ALL** correct answers.)

    A. The use of personal protective equipment by healthcare workers coming into contact with the patient. Correct: there is/are (an) other correct answer(s).
    B. Isolating contaminated patients from other hospital patients. Correct: there is/are (an) other correct answer(s).
    C. Removing the patient's clothing. Correct: there is/are (an) other correct answer(s).
    D. None of the above. Incorrect.

32. Which of the following statements is true about secondary exposure to hazardous substances such as cholinesterase inhibitors? (Choose **ALL** correct answers.)

    A. Healthcare workers can be secondarily exposed to cholinesterase inhibitor poisoning victims due to off-gassing of chemicals on the victims' skin, hair, and clothing. Correct: There is/are (an) other correct answer(s).
    B. Patients with skin exposure should be decontaminated with 0.5% hypochlorite (bleach) solution, rather than water. Incorrect. Water, in most cases, is equally as effective as bleach. The most important factor associated with survival is how rapidly decontamination is carried out.
    C. Indoor decontamination rooms should have independent ventilation to the outside. Correct: There is/are (an) other correct answer(s).
    D. Secondary exposure can result from emesis after ingestion of cholinesterase inhibitors. Correct: There is/are (an) other correct answer(s).
    E. None of the above. Incorrect.

33. The most important aspect of supportive care for cholinesterase inhibitor toxicity is aimed at: (Choose the **ONE BEST** answer.)

    A. The cardiovascular system. Incorrect.
    B. The respiratory system. Correct: Death from cholinesterase inhibitor toxicity is most often due to respiratory failure.
    C. The liver and kidneys. Incorrect.
    D. The digestive tract. Incorrect.
    E. None of the above. Incorrect.

34. Atropine counteracts which of the following effects of cholinesterase inhibitor poisoning. (Choose the **ONE BEST** answer.)

    A. Muscarinic effects. Correct. Atropine competitively occupies the muscarinic binding sites, thus reducing the effects of excessive acetylcholine.
    B. Nicotinic effects. Incorrect. Evidence is lacking to show that atropine counteracts nicotinic effects.
    C. Muscarinic and nicotinic effects. Incorrect. Atropine only counteracts the muscarinic effects.
    D. None of the above. Incorrect.

35. Which of the following is the best end-point for titration of atropine dosage? (Choose the **ONE BEST** answer.)

    A. Pupillary dilation. Incorrect. Pupillary constriction from systemic (as opposed to conjunctival) exposure may be a late finding in cholinesterase inhibitor toxicity. Also, when pupillary constriction does occur, it may be resistant to systemic atropine. Constriction can occur with only local, conjunctival exposure when there is no systemic toxicity. Pupils may be normal or dilated in a significant minority of poisoned patients. Finally, constricted pupils do not kill poisoned patients.
    B. Development of heart-rate >100/min. Incorrect. In some poisoning cases, nicotinic signs predominate over muscarinic signs, leading to tachycardia.
    C. Development of blood pressure > 120/80. Incorrect. In some poisoning cases, nicotinic signs predominate over muscarinic signs, leading to hypertension.
    D. Skin flushing. Incorrect. While skin flushing can occur after atropine administration, the important effect of atropine is to improve oxygenation.
    E. None of the above. Correct: Atropine dose should be titrated to correction of respiratory distress and hypoxia. Therefore, none of the above answers is correct.

36. In cases of suicidal insecticide organophosphorus cholinesterase inhibitor ingestion: (Choose **ALL** correct answers.)

    A. Atropine should be given intravenously, but if an I.V. line cannot be established, it is better to give it I.M. than by autoinjector. Incorrect: Administration by autoinjector is more effective than by the intramuscular route.
    B. Extremely high doses of atropine may be required. Correct: In one case, a patient required 3,600 mg in the first 24 hours, and a total of 30,730 mg over the patient's 35 days of treatment.
    C. Atropine dosage requirements are less than that needed for nerve gas poisoning. Incorrect: Atropine requirements in organophosphorus ingestion can be much higher than for nerve agent poisoning.
    D. Atropine should not be used unless miosis (pupillary constriction) is present. Incorrect: While pupillary constriction occurs in most cases of significant cholinesterase inhibitor poisoning, a substantive minority of cases may have normal or even dilated pupils.
    E. None of the above. Incorrect.

37. Which of the following statements are true about the route of administration of atropine? (Choose **ALL** correct answers.)

    A. The intravenous route is preferred. Correct: There is/are (an) other correct answer (s)
    B. Intramuscular injection provides more rapid onset than the use of an atropine autoinjector. Incorrect: Atropine autoinjectors provide higher blood levels more rapidly than intramuscular injections.
    C. Atropine can be administered by the intraosseous route. Correct: There is/are (an) other correct answer (s)
    D. Atropine can be administered by the intratracheal route. Correct: There is/are (an) other correct answer (s).
    E. None of the above. Incorrect.

38. Which of the following statements are true about 2-PAM (Choose **ALL** correct answers.)

    A. It works by attaching to cholinesterase inhibitors that have blocked cholinesterase, and removing the cholinesterase inhibitor. Correct: There is/are (an) other correct answer (s).
    B. It will not work after "aging" has occurred. Correct: There is/are (an) other correct answer (s).
    C. Its effects are multiplied when atropine is co-administered. Correct: There is/are (an) other correct answer (s).
    D. None of the above. Incorrect.

39. Which of the following delay the onset of cholinesterase inhibitor toxicity as well as the onset of aging (and therefore prolong the period during which 2-PAM is still effective)? (Choose **ALL** correct answers.)

    A. Dermal exposure. Correct: There is/are (an) other correct answer (s).
    B. Exposure to cholinesterase inhibitors which high fat solubility. Correct: There is/are (an) other correct answer (s).
    C. Exposure to cholinesterase inhibitors that do not become toxic until metabolically converted to their active ingredients. Correct: There is/are (an) other correct answer (s).
    D. None of the above. Incorrect.

40. Which of the following statements are true about the treatment of carbamate poisoning? (Choose **ALL** correct answers.)

    A. 2-PAM is contraindicated in all cases of carbamate poisoning. Incorrect: 2-PAM *when given alone*, will decrease survivability only with toxicity due to the carbamate, carbaryl. However, atropine should always be administered along with atropine. When this is done, survivability, even with carbaryl, is improved. (However, at least in animal studies, survival rates are best in *carbaryl* toxicity if atropine is administered without 2-PAM. With other carbamates, 2-PAM alone has either had no effect or has improved outcome.
    B. 2-PAM *plus* atropine has been shown to worsen the outcome in carbamate poisoning due to carbaryl when compared to giving *no* antidote. Incorrect. In carbaryl poisoning in animals, 2-PAM *without* atropine decreased survival (However, 2-PAM should never be given without atropine). Atropine *plus* atropine increased survival 3.5-fold. However, atropine *alone* increased survival 6.6-fold. With most other carbamates, 2-PAM alone either did not change survival or improved it compared to no antidote.
    C. Atropine alone is contraindicated *in all cases* of carbamate poisoning. Incorrect. Atropine is not contraindicated for any cases of clinically significant carbamate toxicity. 2-PAM *alone* is only contraindicated with the carbamate, carbaryl. However, 2-PAM should never be given without atropine. Survivability increases with 2-PAM plus atropine, but is even better with atropine alone, when treating isolated carbaryl poisoning.
    D. None of the above. Correct.

41. Causes of failure with 2-PAM treatment include: (Choose **ALL** correct answers.)

    A. Administration of inadequate doses. Correct: There is/are (an) other correct answer (s).
    B. Aging has already occurred. Correct: There is/are (an) other correct answer (s).
    C. Active cholinesterase inhibitor absorption or redistribution (*e.g.*, from fat tissue) is continuing to occur. Correct: There is/are (an) other correct answer (s).
    D. None of the above. Incorrect.

42. Which of the following statements is true about the use of diazepam for acute cholinesterase inhibitor toxicity? (Choose **ALL** correct answers.)

    A. Diazepam is recommended for severe nerve agent poisoning even in the absence of seizures. Correct: There is/are (an) other correct answer (s).
    B. Current thinking is that CNS damage from acute poisoning with cholinesterase inhibitors is due to seizure activity rather than from a direct toxic effect on brain tissue. Correct: There is/are (an) other correct answer (s).
    C. The likelihood of seizures in acute cholinesterase inhibitor poisoning is greatest in pediatric cases and in severe cases of nerve agent poisoning. Correct: There is/are (an) other correct answer (s).
    D. None of the above. Incorrect.

43. For which of the following treatments is there good evidence that they improve the outcome in cases of acute cholinesterase inhibitor poisoning? (Choose **ALL** correct answers.)

    A. Activated charcoal. Incorrect.
    B. Cathartics. Incorrect.
    C. Syrup of ipecac or gastric lavage. Incorrect.
    D. None of the above. Correct.

44. Which of the following area emergency response agencies should be promptly notified in the event of a cholinesterase inhibitor exposure with the potential for multiple victims? (Choose **ALL** correct answers.)

    A. Area EMS providers. Correct: There is/are (an) other correct answer (s).
    B. Private physicians' offices. Correct: There is/are (an) other correct answer (s).
    C. The local/regional poison center. Correct: There is/are (an) other correct answer (s).
    D. The public health agency. Correct: There is/are (an) other correct answer (s).
    E. None of the above. Incorrect.

45. Which of the following clinical findings are characteristic of intermediate syndrome? (Choose **ALL** correct answers.)

    A. Fasciculations. Incorrect.
    B. Depression or loss of deep tendon reflexes. Correct.
    C. Proximal limb muscle weakness. Correct.
    D. Distal limb muscle weakness. Incorrect.
    E. Weakness of neck flexors. Correct: There are other correct answers, too.
    F. Acute respiratory distress. Correct: There are other correct answers, too.
    G. CNS depression. Incorrect.
    H. Cranial nerve palsies. Correct.
    I. Onset 2-3 weeks after resolution of the acute cholinergic toxidrome. Incorrect. Note that onset of intermediate syndrome between *24-96 hours (1-4 days)* after resolution of the acute cholinergic toxidrome discussed above and the onset of organophosphate-induced delayed neuropathy (OPIDN) which has been reported to occur 1-5 weeks after resolution of the acute toxidrome.
    J. None of the above. Incorrect.

46. The prognosis for intermediate syndrome is (Choose **ALL** correct answers.)

    A. Poor, regardless of treatment. Incorrect. Intermediate syndrome usually resolves spontaneously within 1-2 weeks.
    B. Excellent, with supportive care in the absence of hypoxic damage. Correct.
    C. None of the above. Incorrect. The correct answer is B.

47. In contrast to intermediate syndrome, OPIDN has the following features. (Choose **ALL** correct answers.)

    A. Pain. Correct: There are other correct answers, too.
    B. Paresthesias. Correct: There are other correct answers, too.
    C. Longer time until onset. Correct: There are other correct answers, too.
    D. Progression of findings from peripherally to proximally. Correct: There are other correct answers, too.
    E. Longer duration of clinical abnormalities. Correct: There are other correct answers, too. Correct: There are other correct answers, too.
    F. None of the above. Incorrect.

48. The cause of OPIDN is: (Choose the **ONE BEST** answer.)

    A. Inadequate use of 2-PAM in the cholinergic toxidrome. Incorrect.
    B. Excessive acetylcholine levels. Incorrect.
    C. Unknown. Correct.
    D. None of the above. Incorrect.

49. Effective treatment for OPIDN includes (Choose **ALL** correct answers.)

    A. Neurotarget esterase. Incorrect.
    B. 2-PAM. Incorrect.
    C. Atropine. Incorrect.
    D. None of the above. Correct. There are currently no known specific treatments for this condition. Treatment is supportive.

50. Which of the following is correct about Organophosphorus ester-induced chronic neurotoxicity (OPICN) (Choose **ALL** correct answers.)

    A. It has been established by objective measurement of exposures in humans that this condition occurs with repeated or chronic asymptomatic exposures to cholinesterase inhibitors. Incorrect. Most studies of OPICN have used self-reported recall data to measure exposure, a methodology which has not been shown to be reliable.
    B. Is consistent with damage from seizures and hypoxia. Correct: There is another correct answer, too.
    C. Is controversial. Correct: There is another correct answer, too.
    D. None of the above. Incorrect.

51. Effective treatment for OPICN includes (Choose ALL correct answers)

    A. Neurotarget esterase. Incorrect. Neurotarget esterase is not a treatment.
    B. 2-PAM. Incorrect. Evidence is lacking to show that 2-PAM is effective by the time the diagnosis of OPICN is made.
    C. Atropine. Incorrect. Evidence is lacking to show that atropine is effective by the time the diagnosis of OPICN is made.
    D. None of the above. Correct. There is no known specific treatment for this condition. Treatment is supportive.

52. A causal relationship in humans exists between cholinesterase inhibitor exposure and which of the following (Choose **ALL** correct answers.)

    A. Birth defects. Incorrect.
    B. Cancer. Incorrect: The correct answer is D.
    C. Gulf War Illness. Incorrect.
    D. None of the above. Correct.