

Target Audience: Emergency Medicine Residents, Medical Students

Primary Learning Objectives:

1. Recognize signs and symptoms of diphenhydramine toxicity
2. Describe elimination techniques effective for diphenhydramine toxicity
3. Describe the roles of therapeutic interventions in the patient with diphenhydramine toxicity including the indications, contraindications, and efficacy

Secondary Learning Objectives: detailed technical/behavioral goals, didactic points

1. Describe the pathophysiology of diphenhydramine toxicity
2. Compare diphenhydramine with other anticholinergic overdoses and exposures, especially regarding the differences and similarities in presentation, diagnosis, and management
3. Discuss the management priorities for the emergent stabilization of the patient with an anticholinergic toxidrome
4. Describe the methods used to minimize absorption and enhance elimination of agents in the context of anticholinergic overdose

Critical actions checklist:

1. Obtain an ECG (to rule out wide-complex tachycardia suggesting TCA toxicity)
2. Administer benzodiazepines (for seizures or agitation)
3. Administer physostigmine (for altered mental status)
4. Obtain APAP level
5. Consult Poison Center or toxicologist
6. Admit to the PICU

Environment:

1. Room Set Up – ED critical care area
 - a. Manikin Set Up – Mid or high fidelity simulator
 - b. Props – Standard ED equipment

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CASE SUMMARY

SYNOPSIS OF CASE

This is a case of an otherwise healthy 15-year-old girl who ingests a large number of diphenhydramine tablets in a self-harm attempt. She had a fight with her boyfriend and raided the contents of the medicine cabinet in her home. She ingested the entire bottle of 25mg Benadryl™ (diphenhydramine) tablets, 30 tablets total. Her mother found her acting strangely about 2 hours later and called the paramedics. The patient will not be able to provide a history to explain her symptoms and the mother will not initially know what happened. There are no co-ingestants in the case, but the examiner will have to find a way to get more details from the family about the home environment. She will present with typical anticholinergic signs and symptoms. She will have wide-complex tachycardia and will also have a grand mal seizure. If managed correctly, she will do well with supportive therapy. Physostigmine may be considered, but only after careful exclusion of tricyclic toxicity has been ensured. She will require sodium bicarbonate therapy, seizure control and will need PICU admission.

SYNOPSIS OF HISTORY

She has had a rocky relationship with her boyfriend, Joey, for months. They broke up earlier today at school after an argument. While walking home with a friend, the patient said that she was upset and was thinking of doing something to show her ex-boyfriend how mad she was. When she got home she decided to kill herself by taking an overdose of pills, and diphenhydramine was the only medication she had. She ingested 30 tablets then went to her room. Mom found her acting strangely after she got home from work. No co-ingestants.

SYNOPSIS OF PHYSICAL

She presents via EMS with typical anticholinergic features including flushing, mydriasis, confusion, decreased bowel sounds, combativeness, and dry skin. She is not able to give an accurate history of what happened. She is initially confused and agitated. As part of the case, she will have a seizure, after which she will have typical postictal sedation, but not obtundation and not necessarily require airway protection. She will have urinary retention (750 mL). There will be no evidence of trauma.

SCORING GUIDELINES

The case is intended to test the examinee's understanding of the typical manifestations of diphenhydramine toxicity and the anticholinergic toxidrome. The toxidrome should provide a clue to the etiology of the patient's altered mental status. Ask the learner to describe the symptoms and signs observed. If the learner does not, then the examiner should score down the performance, or make the patient unstable. In addition, the examinee needs to solicit the help from mom (who arrives late) or family/boyfriend (via phone or via mom) for clues at home to suggest the agent responsible for the toxidrome. The use of physostigmine is warranted, however, the examinee needs to first discover that diphenhydramine was the causative agent and discuss with the poison center. If the learner administers physostigmine before either checking an ECG for the QRS interval, or having obtained a clear history of diphenhydramine ingestion, then the patient will become hemodynamically unstable (severe bradycardia) and seize. An ECG must be performed before physostigmine. The examinee should recognize the lack of a significant R wave in lead aVR and should also note a wide complex rhythm. This should prompt the use of sodium bicarbonate. If not, the patient will first develop hemodynamically stable ventricular tachycardia (VT), then pulseless VT. A seizure will occur as part of the natural process, regardless of how well the examinee is doing. Seizures must be

treated with benzodiazepines or they will persist. Phenytoin and other anticonvulsants (e.g., Levetiracetam) will not be effective. Activated charcoal (AC) is reasonable, but only after the airway is protected. If there is an attempt to give AC on arrival, the patient will seize before it can be given. If AC is given after the seizure, while she is postictal, the patient will aspirate. She must be admitted to the PICU. If considering ward admission, the consulting hospitalist will not accept.

CRITICAL ACTIONS

1. Obtain an ECG

Obtain an ECG. Correctly interpret findings. The ECG will be helpful in ruling out a widened QRS complex suggesting TCA toxicity and cardioactive steroid (digoxin-like) effects.

Cueing Guideline: The nurse can ask if the doctor would like an ECG (this prompt can be delivered if the learner requests that the patient be placed on continuous telemetry monitoring).

2. Administer benzodiazepines (for agitation or seizures)

Administer benzodiazepines for agitation or seizures.

Cueing Guideline: Nurse can ask the doctor if anything can be given for the patient's symptoms, as initial empiric interventions are attempted without effect or clinical improvement.

3. Administer physostigmine for altered mental status

Administer physostigmine for altered mental status.

Cueing Guideline: The nurse can ask if the doctor if anything can be given for the patient's symptoms (especially if the learner has identified the anticholinergic toxidrome).

4. Obtain APAP level

Obtain APAP level. Confirm or exclude acetaminophen as a co-ingestant. The learner fulfills this critical action by ordering the appropriate lab tests.

Cueing Guideline: The nurse can ask if the doctor would like additional diagnostic tests to help rule-in or rule-out possible etiologies for the patient's symptoms.

5. Consult Toxicology

Consult Toxicology (either the Poison Center or a consultant in toxicology)

Cueing Guideline: Nurse can ask the doctor if anyone has called the Toxicologist yet. Nurse may also ask if there is anything more we can do to help improve the patient's condition and (if the etiology is known) eliminate or neutralize the diphenhydramine.

6. Admit to the PICU

Admit to the PICU. Patient will not be stable for any other destination.

Cueing Guideline: Nurse can ask the doctor if anyone has called the pediatric intensivist to arrange for a definitive disposition decision.

Critical Actions Checklist¹

Resident Name								
Case Description								
Skills measured <small>Core competencies: PC Patient care, MK Medical knowledge, IC Interpersonal and communication skills, P Professionalism, PB Practice-based learning and improvement, SB Systems-based practice</small>	Very Unacceptable		Unacceptable		Acceptable		Very Acceptable	
Data Acquisition (D) PC MK I	1	2	3	4	5	6	7	8
Problem Solving (S) PC MK PB	1	2	3	4	5	6	7	8
Patient Management (M) PC MK IC P PB SB	1	2	3	4	5	6	7	8
Resource Utilization (R) PC PB SB	1	2	3	4	5	6	7	8
Health Care Provided (H) PC SB	1	2	3	4	5	6	7	8
Interpersonal Relations (I) IC P	1	2	3	4	5	6	7	8
Comprehension of Pathophysiology (P) MK PB	1	2	3	4	5	6	7	8
Clinical Competence (C) PC MK IC P PB SB	1	2	3	4	5	6	7	8
Critical Actions								
Yes	No				Comments:			
		Obtain an ECG						
		Administer benzodiazepines for agitation or seizure						
		Administer physostigmine for altered mental status						
		Obtain APAP level						
		Consult Toxicology						
		Admit to the PICU						
		Yes	No					
				Dangerous actions				

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¹ Modified ABEM Oral Certification Examination checklist and scoresheet

HISTORY

Age: 15

Sex: Female

Name: Sarah Drill

Method of Transportation: Ambulance

Person giving information: EMS, patient (incomprehensible), mom or whoever is available via phone.

Onset and Description of Complaint: Patient found acting strangely just before arrival.

Chief Complaint: Altered mental status.

Past Medical Hx: Negative

Habits: Hanging out at the mall, texting on her smart phone.

Family Med Hx: HTN, Diabetes.

Social Hx: No known history of smoking, drugs, or alcohol use.

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PLAY OF CASE GUIDELINES

This is a case of an otherwise healthy 15-year-old girl who ingests a large number of diphenhydramine tablets in a self-harm attempt. She had a fight with her boyfriend and raided the contents of the medicine cabinet in her home. She ingested the entire bottle of 25mg Benadryl™ (diphenhydramine) tablets (30 tablets total). Her mother found her acting strangely about 2 hours later and called the paramedics.

1. The patient will not be able to provide a history to explain her symptoms and the mother will not initially know what happened.
2. There are no co-ingestants in the case, but the examiner will have to find a way to get more details from the family about the home environment.
3. She will present with typical anticholinergic signs and symptoms.
4. She will have wide-complex tachycardia and will also have a grand mal seizure.
5. If managed correctly, she will do well with supportive therapy. Physostigmine may be considered, but only after careful exclusion of tricyclic antidepressant (TCA) toxicity has been ensured.
6. ECG demonstrates sinus tachycardia without QRS widening. IV fluid therapy and benzodiazepines (required to treat the central anticholinergic syndrome) are the only necessary treatment for these ECG findings.
7. The patient requires seizure control and PICU admission for continued observation and serial reassessments.

Required Actions within the First Two Minutes

- Point-of-care glucose ordered (patient with altered mental status)
- Peripheral IV access ordered/inserted and fluid boluses started
- ABG/VBG, electrolytes, other diagnostics, and ECG are ordered
- Initial (empiric) supportive interventions for airway, breathing, circulation, and mental status until anticholinergic toxidrome is deduced, recognized, or confirmed by history
- Seizures, if part of the play of case, should be treated with benzodiazepines

Branch Points

- **IF NO POINT-OF-CARE GLUCOSE IS ORDERED WITHIN THE FIRST TWO MINUTES, patient becomes more confused and obtunded and A NEW SEIZURE WILL BE TRIGGERED.**
- **INITIAL EMPIRIC INTERVENTIONS DIRECTED AT THE TACHYCARDIA (E.G. IV FLUIDS, BENZODIAZEPINES) WILL HELP IMPROVE THE HEART RATE.**
- **IF THE PATIENT'S AGITATION WORSENS AND A BENZODIAZEPINE IS GIVEN,** the patient's agitation (and tachycardia) will improve.
- **IF THE PATIENT SEIZES AND BENZODIAZEPINES ARE GIVEN,** then the seizure will stop.
- **IF PHYSOSTIGMINE IS GIVEN,** anticholinergic symptoms (tachycardia, delirium, etc.) will improve.

Required Actions over the Next Four Minutes

- Anticholinergic toxidrome should be recognized by this time
- Diagnostics should be returned as ordered
- Seizures and agitation, if present earlier in the case, should be treated by this time
- PICU consultation for definitive disposition and placement

PHYSICAL EXAM

Vital Signs: BP: 140/90 mmHg P: 135/minute R: 18/minute T: 40.5C (104.9F)
POx: 98%

General Appearance: Awake, alert, slightly mottled

HEENT: AT/NC. Pupils 6mm, not reactive to light. EOMI without nystagmus. Dry mouth. Supple.

Lungs: Clear

CV: Tachycardic, regular. Normal perfusion.

Abdomen: Soft, bladder fullness and tenderness, absent bowel sounds.

Extremities: Atraumatic. No edema.

Rectal: Hem negative stools.

Pelvic: Deferred.

Back: Atraumatic.

Neurological: Awake. Follows commands intermittently. Easily startled. Incoherent words. Moves all extremities equally. No focal deficits. Normal reflexes. No myoclonus or clonus.

Skin: Flushed, dry.

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STIMULUS INVENTORY

- #1 Complete blood count
- #2 Basic metabolic panel
- #3 Urinalysis
- #4 Liver function tests
- #5 Arterial blood gas
- #6 Creatinine phosphokinase
- #7 Toxicology / Urine drug screen
- #8 Coagulation studies
- #9 Point-of-care serum glucose
- #10 US bladder
- #11 Lactate
- #12 Urine pregnancy

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LAB DATA & IMAGING RESULTS

Stimulus #1	
Complete Blood Count (CBC)	
WBC	12,000/mm ³
Hemoglobin	12.5 g/dL
Hematocrit	36%
Platelets	115,000/mm ³
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2	
Basic Metabolic Profile (BMP)	
Sodium	135mEq/L
Potassium	4.0mEq/L
Chloride	104 mEq/L
Bicarbonate	22 mEq/L
Glucose	98 mg/dL
BUN	25 mg/dL
Creatinine	1.1 mg/dL

Stimulus #3	
Urinalysis	
Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Negative
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0-2/hpf
RBC	0-2/hpf

Stimulus #4	
Liver Function Tests	
AST	35 U/L
ALT	38 U/L
Alk Phos	60 U/L
T. Bilirubin	0.8 mg/dL
Albumin	4 mg/dL
Protein	7 mg/dL

Stimulus #5	
Arterial Blood Gas	
pH	7.34
pCO ₂	36 mm Hg
pO ₂	90 mm Hg
HCO ₃	22 mEq/L
SaO ₂	97% (FiO ₂ =0.21)

Stimulus #6	
Creatine phosphokinase	
CPK	80 U/L

Stimulus #7	
Toxicology	
Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	Undetectable
Urine drug screen	
Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCA's	Negative
THC	Negative

Stimulus #8	
Coagulation Studies	
INR	1.0
PTT	32 seconds

Stimulus #9	
Point-of-care serum glucose	
98 mg/dL	

Stimulus #10	
US bladder	750 mL

Stimulus #11	
Lactate	1.8 mmol/L

Stimulus #12	
Urine pregnancy	Negative

Stimulus #1**Complete Blood Count (CBC)**

WBC	12,000/mm ³
Hemoglobin	12.5 g/dL
Hematocrit	36%
Platelets	115,000/mm ³
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2**Basic Metabolic Profile (BMP)**

Sodium	135mEq/L
Potassium	4.0mEq/L
Chloride	104 mEq/L
Bicarbonate	22 mEq/L
Glucose	98 mg/dL
BUN	25 mg/dL
Creatinine	1.1 mg/dL

Stimulus #3**Urinalysis**

Color	Yellow
Specific gravity	1.030
Glucose	Negative
Protein	Negative
Ketones	Negative
Leuk. Esterase	Negative
Nitrites	Negative
WBC	0-2/hpf
RBC	0-2/hpf

Stimulus #4**Liver Function Tests**

AST	35 U/L
ALT	38 U/L
Alk Phos	60 U/L
T. Bilirubin	0.8 mg/dL
Albumin	4 mg/dL
Protein	7 mg/dL

Stimulus #5**Arterial Blood Gas**

pH	7.34
pCO ₂	36 mm Hg
pO ₂	90 mm Hg
HCO ₃	22 mEq/L
SaO ₂	97% (FiO ₂ =0.21)

Stimulus #6

Creatine phosphokinase

CPK	80 U/L
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Stimulus #7**Toxicology**

Salicylate	< 4 mg/dL
Acetaminophen	< 10 mcg/mL
Ethanol	Undetectable

Urine drug screen

Amphetamines	Negative
Benzodiazepines	Negative
Cocaine	Negative
Opiates	Negative
TCAs	Negative
THC	Negative

Stimulus #8

Coagulation Studies

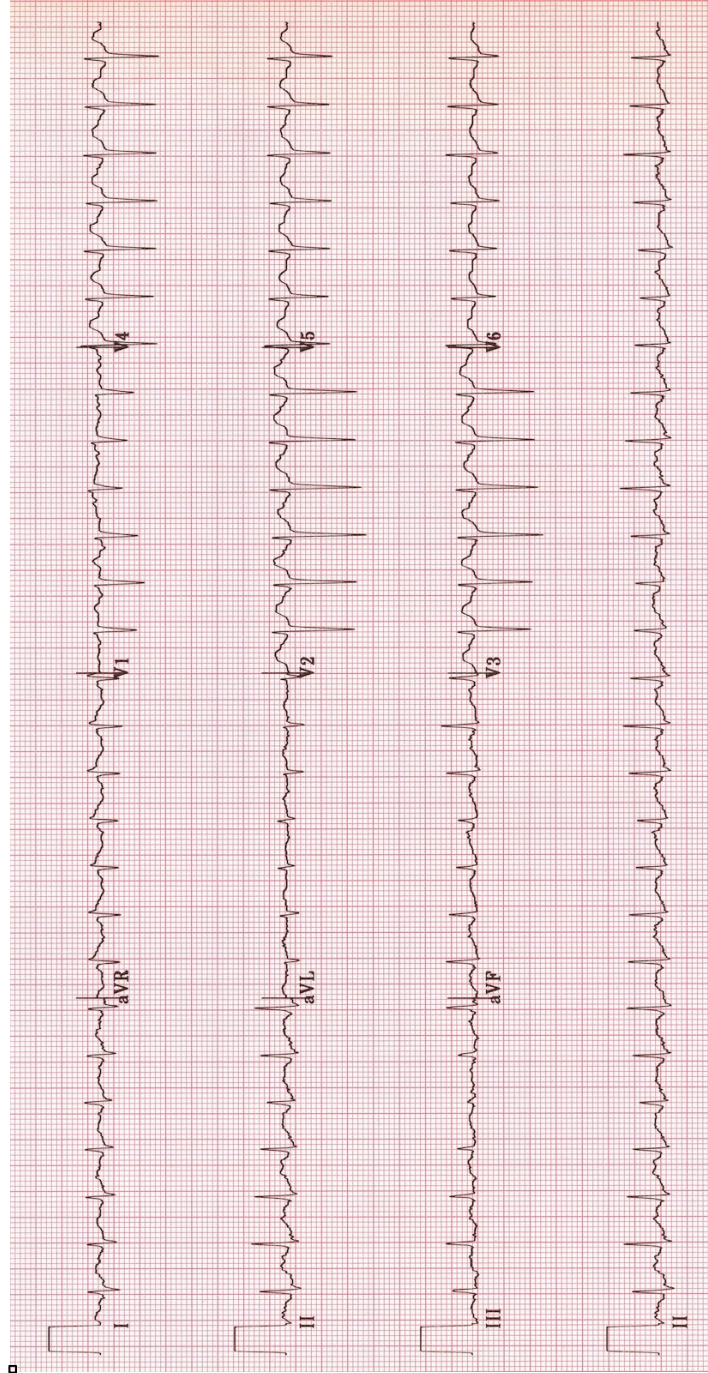
INR	1.0
PTT	32 seconds

Stimulus #9

Serum glucose

98 mg/dL

Stimulus #10



Teaching Points: Diphenhydramine Toxicity

Uses Diphenhydramine (Benadryl) is a sedating antihistamine medication with anticholinergic, antitussive, antiemetic, and local anesthetic properties. The FDA-approved indications for its use include allergic rhinitis, anaphylaxis, insomnia, motion sickness, Parkinsonism, and urticaria. Diphenhydramine is widely available in nonprescription preparations.

Mechanism of toxicity Diphenhydramine antagonizes histamine-induced responses at H1 receptors, thereby causing smooth muscle relaxation, decreased capillary permeability, and preventing urticaria. Sedation occurs due to antagonism of H1 receptors in the brain and central muscarinic effects. In overdose, the clinical effects are usually dose-dependent. The effects are largely an extension of the adverse effects seen in therapeutic doses: CNS depression and anticholinergic excess. Extremely large doses can cause seizures and sodium channel blockade in the heart.

Pharmacokinetics Diphenhydramine can be administered orally, intramuscularly, or intravenously. It is well absorbed orally, achieving peak concentrations within 2-3 hours. When given intravenously, maximal effect occurs at 1 hour. The serum half-life is 3-7 hours with a duration of action up to 24 hours in therapeutic doses. Diphenhydramine is metabolized hepatically.

Toxic Dose The therapeutic adult dose is 25-50 mg po every 4-8 hours. Severe toxicity typically develops after ingestion of more than 1 gram. Deaths in adults have been reported after ingestion of 25mg/kg.

Clinical presentation The clinical effects of diphenhydramine overdose are dose dependent. The effects are largely an extension of the adverse effects seen in therapeutic doses: CNS depression, anticholinergic excess (hyperthermia, dry mucous membranes, mydriasis, tachycardia, slowed GI motility, urinary retention). Extremely large doses can cause seizures. The ECG may exhibit findings like a tricyclic antidepressant overdose, however, this is uncommon. A sinus tachycardia may be present due to anticholinergic effects. There may be a large terminal R in lead AVR. Sodium channel blockade may occur causing a prolonged QTc, widened QRS, and dysrhythmias. The urine toxicology screen may be falsely positive for tricyclic antidepressants.

Decontamination and Enhanced Elimination

- 1) Charcoal - Binds diphenhydramine. Administer charcoal if the patient has a normal mental status.
- 2) Multidose charcoal - May have a role in the setting of a large overdose because the GI tract will be slowed from the anticholinergic effects, thereby slowing absorption of drug.
- 3) Gastric lavage - May be considered for the patient who presents early with a massive diphenhydramine overdose as these patients are at a high risk for seizures and cardiac dysrhythmias. Reducing absorption of the drug may prevent these sequelae.
- 4) Hemodialysis - Diphenhydramine is not effectively removed by hemodialysis.

Treatment

- 1) CNS effects
 - a. Somnolence - Intubate if the patient is unable to protect the airway.

- b. Agitation – May occur from the anticholinergic effects. Treat with benzodiazepines, titrate to effect. Intubate if necessary.
 - c. Seizures – May occur in large overdose. Treat with benzodiazepines. If refractory seizures, consider barbiturates or propofol.
- 2) Cardiovascular effects
- a. Tachycardia - Due to agitation and anticholinergic effects on the muscarinic receptors of the heart. Treat with fluids, benzodiazepines for agitation.
 - b. Blood pressure effects-
 - i. Hypertension may occur because of agitation. Treat with benzodiazepines.
 - ii. Hypotension - Less common, but may occur as a result of peripheral alpha-receptor blockade. Treat with fluids, pressors if necessary.
 - c. Prolonged QTc – Usually not of clinical significance. Monitor electrolytes, check serial ECGs.
 - d. Widened QRS interval - Due to Na-channel blockade in the heart. Treat with bicarbonate boluses of 1-2 amps IVP (for peds, 1-2mEq/kg). Check serial ECGs.
 - e. Wide complex dysrhythmias - Usually the sequelae of Na-channel blockade. Treat with bicarbonate as above and ACLS protocols.
- 3) Hyperthermia - May occur in the setting of extreme, prolonged agitation in combination with decreased ability to sweat from the anticholinergic effects on the sweat glands. Check rectal temps in patients with significant agitation.
- a. Treat agitation with benzodiazepines.
 - b. Intubate, sedate, and paralyze if necessary.
 - c. Active cooling measures may also be indicated, such as ice packs.
- 4) Rhabdomyolysis - May occur in the setting of extreme, prolonged agitation, or seizures. Check a CK.
- a. Follow serial CK levels, creatinine, and electrolytes.
 - b. Hydrate with 0.9NS.

Antidotes Physostigmine (Antilirium) - This drug is used to reverse the effects of anticholinergic toxicity. It is a carbamate that acts by reversibly inhibiting acetylcholinesterase, the enzyme that degrades acetylcholine. The net effect is an increase of acetylcholine at the central and peripheral muscarinic and nicotinic receptors. It may be used as a diagnostic agent when trying to differentiate the cause of a patient with altered mental status in whom an anticholinergic toxidrome is suspected. The administration of physostigmine has been associated with dysrhythmias and seizures, particularly in the setting of tricyclic antidepressant overdose. Therefore, it is recommended to check a patient's ECG for signs of TCA drug effect (>3mm R in AVR, widened QRS) before administering physostigmine. The dose is 0.5-2.0mg IVP slowly over 1-2 minutes. Atropine should be kept at the bedside to treat bradycardia. The duration of action of physostigmine is 20-30 minutes, so the anticholinergic signs and symptoms may return.

Prognosis Most patients recover completely with good symptomatic and supportive care. Death after diphenhydramine overdose is rare but may occur in the setting of a large overdose.

References

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