Diphenhydramine-Acetaminophen Overdose
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Target Audience: Emergency Medicine Residents, Medical Students

Comment [MC1]: Previously titled anticholinergic toxicity case

Primary Learning Objectives:

1. Recognize signs and symptoms of diphenhydramine toxicity
2. Discuss the ubiquitous availability of drugs like diphenhydramine and acetaminophen in over-the-counter preparations that make them likely co-toxicants in intentional ingestions
3. Describe elimination techniques effective for diphenhydramine toxicity
4. 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 25-year-old woman brought to the ED by EMS after her roommate found her acting oddly. The roommate says the patient has been under a lot of stress and having trouble sleeping. The roommate doesn't know what medications the patient is taking. EMS could not find any bottles near the patient. The roommate said she would go home to try to look for any drugs or medications.

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 her roommate, 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/acetaminophen (Tylenol PM®) was the only medication she had. She ingested 30 tablets (25/325mg) then went to her room. Her roommate found her acting strangely after she got home from work later that evening (6 hours after last seen normal). No other co-ingestants.

SYNOPSIS OF PHYSICAL

This patient presents with typical anticholinergic features:

- Dry, flushed skin (no diaphoresis)
- Mydriasis (7mm pupils)
- Altered mental status, combativeness, and confusion (answers only to name, mumbles, appears to be responding to internal stimuli)
- Urinary retention (750 mL of urine in the bladder)
- No evidence of trauma

She is not able to give an accurate history of what happened. She is initially confused and agitated.

As the case progresses, she will seize, after which she will have typical postictal sedation. As the case progresses, she will not necessarily require airway protection (this feature may be added to the case at the discretion of faculty).

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CRITICAL ACTIONS

1. **Administer IV crystalloid fluids**

   Administer IV crystalloid fluids, preferably as boluses at the beginning of the case.
   Cueing Guideline: The nurse can ask if the doctors wants an IV placed and IV fluids started (nurse should specific the fluid type).

2. **Obtain an ECG**

   Obtain an ECG. Correctly interpret findings. The ECG will be helpful in ruling out other toxicities (e.g., TCA).
   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 telemetric monitoring).

3. **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.

4. **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).

5. **Obtain APAP level**

   Obtain APAP level. Confirm or exclude acetaminophen as a co-toxicant. 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.

6. **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.

7. **Administer N-acetylcysteine**

   Administer N-acetylcysteine (150 mg/kg initial dose) for transaminitis and coexistent acetaminophen toxicity.
   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 transaminitis and exposure to acetaminophen).

8. **Admit to the MICU**

   Admit to the MICU. 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 Checklist[1]

Resident Name	
Case Description	

Skills measured **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	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:
		Administer IV crystalloid fluids	
		Obtain an ECG	
		Administer benzodiazepines for agitation or seizure	
		Administer physostigmine for altered mental status	
		Obtain APAP level	
		Administer N-acetylcysteine	
		Consult Toxicology	
		Admit to the MICU	

Yes	No	
		Dangerous actions

[1] Modified ABEM Oral Certification Examination checklist and scoresheet

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HISTORY

Age: 25

Sex: Female

Name: Laura Wild

Method of Transportation: Ambulance

Person giving information: EMS, patient (incomprehensible), roommate

Chief Complaint: Altered mental status.

Onset and Description of Complaint: Patient found acting strangely just before arrival. The roommate says the patient has been under a lot of stress and having trouble sleeping. The roommate doesn't know what meds the patient is taking. EMS could not find any bottles near the patient. The roommate said she would go home to try to look for any drugs or medications.

Past Medical Hx: Unknown (none if roommate is asked)

Family Med Hx: Unknown (roommate will not be able to contribute data for questions about the family history)

Social Hx: No tobacco use
Social alcohol use observed by roommate
No observed recreational drug use reported by roommate

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PLAY OF CASE GUIDELINES

This is a case of a 25-year-old woman is brought in by EMS after her roommate found her acting oddly. **The roommate says the patient has been under a lot of stress and having trouble sleeping.** The roommate doesn't know what meds the patient is taking. EMS could not find any bottles near the patient. The roommate said she would go home to try to look for any drugs or medications.

1. The patient will not be able to provide a history to explain her symptoms and the roommate will not know what happened.

2. Acetaminophen is a co-toxicant in the case.

3. The patient presents with typical anticholinergic signs and symptoms.

4. The patient seizes during the case.

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 MICU admission for continued observation and serial reassessments.

PHYSICAL EXAM

Vital Signs: BP: 136/86 mmHg P: 130/minute R: 18/minute T: 38.3C (101F) POx: 99%

General Appearance: Awake but confused, agitated, and with altered mental status

HEENT: AT/NC. Pupils 7 mm, not reactive to light. EOMI without nystagmus. Dry mouth. Supple neck.

Lungs: Clear to auscultation. No wheezes, rales, or rhonchi.

CV: Tachycardic, regular. No murmurs. Normal perfusion.

Abdomen: Soft, non-tender and non-distended throughout abdomen except over suprapubic area. Positive slight bladder fullness. Minimal suprapubic tenderness. Absent bowel sounds.

Extremities: Atraumatic. No edema.

Rectal: Heme negative stools.

Pelvic: Deferred.

Back: Atraumatic.

Neurological: Awake. Follows commands intermittently, and is therefore uncooperative with complete neurologic evaluation. Easily startled. Tries to get off the stretcher. Incoherent words. Picking at the air (grabbing for imaginary objects, responding to internal stimuli). Moves all extremities equally. No focal deficits. Brisk reflexes. No myoclonus or clonus. If asked to walk, patient is able to weight bear (required assistance) and demonstrates ataxia.

Skin: Warm, flushed, dry.

Required Actions within the First Two Minutes

- Point-of-care glucose ordered (patient with altered mental status); FS= 126 mg/dL
- Peripheral IV access ordered/inserted and fluid boluses started
- ABG/VBG, electrolytes, other diagnostics, and ECG ordered
- Initial (empiric) supportive interventions for airway, breathing, circulation, and mental status until anticholinergic toxidrome is deduced, recognized, or confirmed by history
- Seizures, if selected to begin this early in 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 **WILL BEGIN TO SEIZE**.
- **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.

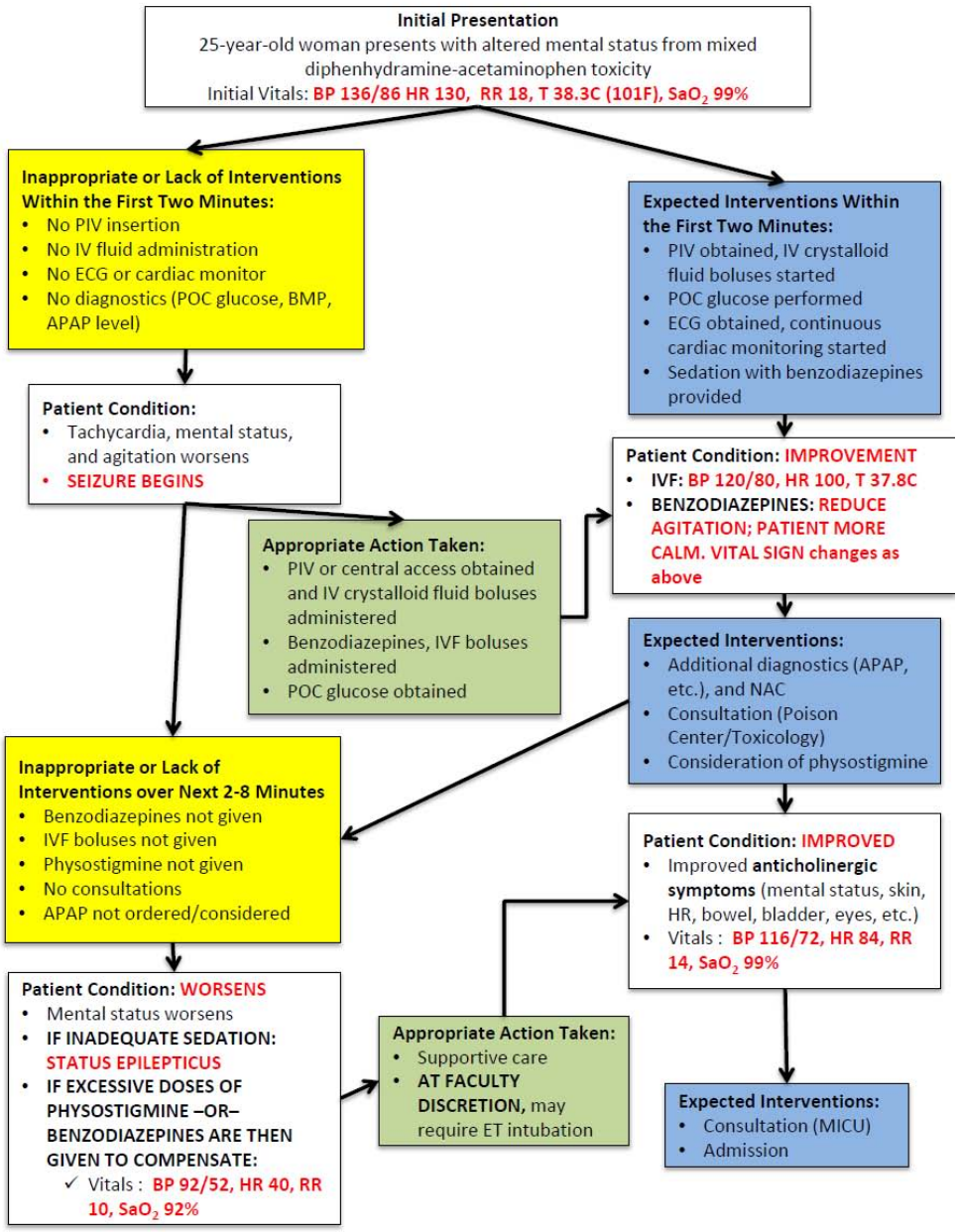
Required Actions over the Next Four Minutes

- Anticholinergic toxidrome should be recognized by this time
- Possibility of co-toxicants (e.g., acetaminophen) should be considered at this time
- Diagnostics should be returned as ordered
- N-acetylcysteine should be administered at this time for elevated APAP level
- Seizures and agitation, if present earlier in the case, should be treated by this time
- MICU consultation for definitive disposition and placement

Branch Points

- **AT FACULTY DISCRETION, IF EXCESSIVE DOSES OF PHYSOSTIGMINE ARE GIVEN DURING THE CASE WITHOUT CONSULTATION WITH OF THE POISON CENTER/TOXICOLOGIST,** then the patient will demonstrate bradycardia, mild hypotension, and sedation (HR 40/minute, BP 92/52 mmHg)

Timeline and Branch Points for This Case



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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	14,000/mm^3
Hemoglobin	13 g/dL
Hematocrit	36%
Platelets	286,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2	
Basic Metabolic Profile (BMP)	
Sodium	140 mEq/L
Potassium	3.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	24 mEq/L
Glucose	126 mg/dL
BUN	23 mg/dL
Creatinine	0.7 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 (pre-seizure)	
CPK	80 U/L

Stimulus #7	
Toxicology	
Salicylate	< 4 mg/dL
Acetaminophen	150 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
Point-of-care serum glucose
126 mg/dL

Stimulus #10	
US bladder	750 mL

Stimulus #11 (pre-seizure)	
Lactate	1.8 mmol/L

Stimulus #12	
Urine pregnancy	Negative

Stimulus #1

Complete Blood Count (CBC)

WBC	14,000/mm^3
Hemoglobin	13 g/dL
Hematocrit	36%
Platelets	286,000/mm^3
Differential	
PMNLs	80%
Lymphocytes	9%
Monocytes	7%
Eosinophils	4%

Stimulus #2

Basic Metabolic Profile (BMP)

Sodium	140 mEq/L
Potassium	3.8 mEq/L
Chloride	98 mEq/L
Bicarbonate	24 mEq/L
Glucose	126 mg/dL
BUN	23 mg/dL
Creatinine	0.7 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	150 mcg/mL
Ethanol	Undetectable

Urine drug screen

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

Stimulus #8

Coagulation Studies

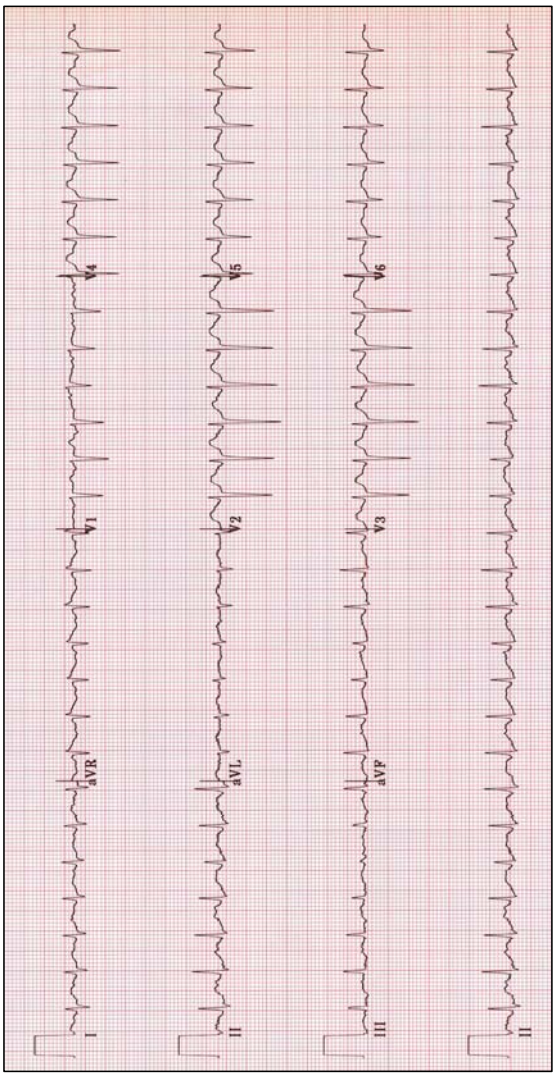
INR	1.0
PTT	32 seconds

Stimulus #9

Serum glucose

126 mg/dL

Stimulus #10



Debriefing Notes: 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 EKG may exhibit findings similar to a tricyclic antidepressant overdose. 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- Charcoal binds diphenhydramine. Administer charcoal if the patient has a normal mental status.
2) Multi-dose 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 their 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 as a result 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 by 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.

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