

ANTICHOLINERGIC DRUG TOXICITY

ANTICHOLINERGICS

- **Anticholinergic intoxication can occur with a wide variety of prescription and over-the counter medications.**
- **Common drugs that have anticholinergic activity include antihistamines, antipsychotics, antispasmodics, skeletal muscle relaxants, and tricyclic antidepressants.**



MECHANISM OF TOXICITY

- Anticholinergic agents competitively antagonize the effects of acetylcholine at peripheral muscarinic and central receptors. Exocrine glands, such as those responsible for sweating and salivation, and smooth muscle are mostly affected. The inhibition of muscarinic activity in the heart leads to a rapid heartbeat. Tertiary amines such as atropine are well absorbed centrally, whereas quaternary amines such as glycopyrrolate have a less central effect.

PHARMACOKINETICS

Absorption may be delayed because of the pharmacologic effects of these drugs on GI motility.

The duration of toxic effects can be prolonged (eg, benztropine intoxication may persist for 2–3 days).



CLINICAL PRESENTATION

The anticholinergic syndrome is characterized by dry skin; dry mouth; mydriasis; tachycardia; and urinary retention. Hyperthermia, coma, and respiratory arrest may occur. Seizures are rare with pure antimuscarinic agents, although they may result from other pharmacologic properties of the drug (eg, tricyclic antidepressants and antihistamines).



Diagnosis

Diagnosis is based on a history of exposure and the presence of typical features, such as dilated pupils and flushed skin. A trial dose of physostigmine can be used to confirm the presence of anticholinergic toxicity; rapid reversal of signs and symptoms is consistent with the diagnosis. Concentrations in body fluids are not generally available.

Useful laboratory studies include electrolytes, glucose, creatine kinase (CK), arterial blood gases, and ECG monitoring.



Treatment

Initial assessment and stabilization are required: Ensure that breathing is present and maintained also assess circulation and initiate cardiac and pulse monitoring.

GI decontamination with activated charcoal is recommended.

Ventricular arrhythmias can be treated with lidocaine.

Manage seizures with benzodiazepines.



The antidote for anticholinergic toxicity is physostigmine salicylate. Physostigmine is the only reversible acetylcholinesterase inhibitor capable of directly antagonizing the CNS manifestations of anticholinergic toxicity; it is an uncharged tertiary amine that efficiently crosses the blood brain barrier. By inhibiting acetylcholinesterase, the enzyme responsible for the hydrolysis of acetylcholine, an increased concentration of acetylcholine augments stimulation at muscarinic and nicotinic receptors. Physostigmine can reverse the central effects of coma, seizures, hallucinations, agitation, and respiratory depression.



Allergy Medicines And Cough Suppressant Toxicity

They are widely used and favored by medical professionals and parents. Because these medications are available over-the-counter (OTC) and are they are frequently implicated in toxic ingestions, particularly in children.

The principal active ingredients in cough and cold medications are antihistamines, decongestants, and antitussives.



ANTI-HISTAMINES

Antihistamines (H₁ receptor antagonists) are commonly found in over-the-counter and prescription medications used for motion sickness, itching, and cough and cold palliation and used as sleep aids.

Acute intoxication with antihistamines results in symptoms very similar to those of anticholinergic poisoning. H₂ receptor blockers (cimetidine, ranitidine, and famotidine) inhibit gastric acid secretion but otherwise share no effects with H₁ agents, do not produce significant intoxication.



MECHANISM OF TOXICITY

H₁ blocker antihistamines are structurally related to histamine and antagonize the effects of histamine on H₁ receptor sites. They have anticholinergic effects (except the “nonsedating” agents: desloratadine, and loratadine).

Some agents (eg, diphenhydramine) have local anesthetic and membrane-depressant effects in large doses.



PHARMACOKINETICS

Drug absorption may be delayed because of the pharmacologic effects of these agents on the GI tract. Volumes of distribution are generally large (3–20 L/kg). Elimination half-lives are highly variable, ranging from 1–4 hours for diphenhydramine to 7–24 hours for many of the others.



CLINICAL PRESENTATION

An overdose results in many symptoms similar to those of anticholinergic poisoning: drowsiness, dilated pupils, flushed dry skin, fever, tachycardia, delirium, hallucinations. Convulsions, rhabdomyolysis, and hyperthermia may occur with a serious overdose, and complications such as renal failure has been reported.

Massive diphenhydramine overdoses have been reported to cause QRS widening and myocardial depression, similar to tricyclic antidepressant overdoses. QT-interval prolongation and torsade-type atypical ventricular tachycardia have been associated with elevated serum levels of terfenadine or astemizole.



TREATMENT

A. Emergency and supportive measures

- 1. Maintain an open airway and assist ventilation if necessary.**
 - 2. Treat seizures, hyperthermia if they occur.**
 - 3. Monitor the patient for at least 6–8 hours after ingestion.**
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- B. Specific drugs and antidotes.** There is no specific antidote for antihistamine overdose. As for anticholinergic poisoning, physostigmine has been used. However, because antihistamine overdoses carry a greater risk so physostigmine is not recommended routinely. Sodium bicarbonate 1–2 mEq/kg IV, may be useful for myocardial depression and QRS-interval prolongation after a massive diphenhydramine overdose.
- C. Decontamination:** Administer activated charcoal orally. Gastric lavage is not necessary after small-to-moderate ingestions if activated charcoal can be given promptly. Because of slowed GI motility, gut decontamination procedures may be helpful, even in late-presenting patients.
- D. Enhanced elimination.** Hemodialysis, hemoperfusion, peritoneal dialysis, and repeat-dose activated charcoal are not effective in removing antihistamines.
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ANTITUSSIVES

Dextromethorphan is a common antitussive agent found in many over-the-counter (OTC) cough and cold preparations. Dextromethorphan is often found in combination products containing antihistamines, decongestants, or acetaminophen.

Dextromethorphan is well tolerated at therapeutic doses, and serious toxicity rarely occurs, even with moderate-to-high doses. However, major toxicity have been reported more commonly by coingestants. Intentional abuse, especially among adolescents and young adults, has been a continuing problem owing to the hallucinogenic potential at high doses.



MECHANISM OF TOXICITY

Dextromethorphan is structurally related to opioids and it has antitussive activity approximately equal to that of codeine.

Dextromethorphan is metabolized in the liver by CYP2D6 to dextrorphan. Both dextromethorphan and dextrorphan antagonize N-methyl-D-aspartate (NMDA) glutamate receptors.

Dextromethorphan and dextrorphan inhibit reuptake of serotonin and may lead to serotonin syndrome especially in patients taking agents that increase serotonin levels, such as SSRI and MAOI. Serotonergic effects, as well as NMDA glutamate receptor inhibition responsible for acute and chronic abuse potential of dextromethorphan.



TOXIC DOSE

Moderate symptoms usually occur when the amount of dextromethorphan exceeds 10 mg/ kg.

Severe poisoning is associated with ingestions of more than 20–30 mg/kg.

The usual recommended adult daily dose of dextromethorphan is 60–120 mg/d; children age 2–5 years can be given up to 30 mg/d.



CLINICAL PRESENTATION

- A. Mild-to-moderate intoxication.** Nausea, vomiting, tachycardia, hypertension, agitation, euphoria, and auditory and visual hallucinations have been reported.
 - B. Severe poisoning.** Disorientation, psychosis, dissociative hallucinations, seizures, coma, QT prolongation, respiratory depression, pulmonary and cerebral edema, and death can occur.
 - C. Serotonin syndrome.** Severe hyperthermia, muscle rigidity, altered mental status, and hypertension may occur.
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TREATMENT

- A. **Emergency and supportive measures.** Most patients with mild symptoms (ie, restlessness, ataxia, or mild drowsiness) can be observed for 4–6 hours and discharged if their condition is improving.
- B. **Specific drugs and antidotes.** Although naloxone has been reported to be effective in doses of 0.06–0.4 mg, other cases have failed to respond to doses up to 2.4 mg.
- C. **Decontamination.** Administer activated charcoal orally. Gastric lavage is not necessary after small-to-moderate ingestions if activated charcoal can be given.
- D. **Enhanced elimination.** The volume of distribution of dextromethorphan is very large, and there is no role for enhanced removal procedures.



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