Overdose and Side Effects of Cholinomimetic Agents – ANS Pharmacology

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Toxicology of cholinomimetics, especially nicotine and cholinesterase inhibitors, is important for clinical implications. In this article, clinical features of adverse effects, resulting from acute and chronic exposures to cholinomimetics, are described. Management of poisoning, including the role of atropine and cholinesterase reactivators, is also discussed.

Overview of Toxicity of Cholinomimetic Activators

Cholinomimetics, especially some **organophosphates**, are used as **insecticides in agriculture,** and accidental poisoning can occur. They are also used for purposes of homicide, suicide, warfare, or chemical terrorism. Therefore, it is essential to understand their toxicology and learn to suspect, diagnose, and manage poisoning with these agents.

Here is a quick review of Cholinergic Agents: (See also Cholinomimetic Agents – ANS Pharmacology)

Direct-acting cholinomimetics directly stimulate the receptors, while indirect-acting cholinomimetics block the action of cholinesterase, thus allowing the persistence of acetylcholine on the receptor.

Direct-acting nicotinic or muscarinic stimulants

These act by stimulating the **nicotinic or muscarinic** receptors.

Choline esters

- Acetylcholine (all acetylcholine receptors)
- Bethanechol (M3 receptors)
- Carbachol (all muscarinic receptors and some nicotinic receptors)
- Methacholine (all muscarinic receptors)

Plant alkaloids

- Arecoline
- Nicotine
- Muscarine
- Pilocarpine (M3 receptors)

A mnemonic for signs and symptoms of acute organophosphate poisoning:

DUMBBELLS: Diarrhea, Urination, Miosis, Bronchospasm, Bradycardia, Excitation of skeletal muscles and CNS, Lacrimation, Salivation, Sweating

Another commonly used mnemonic is **SLUDGE** (or SLUDGEM, where M stands for miosis) for salivation, lacrimation, urination, defecation, gastrointestinal distress, and emesis. These mnemonics help one to remember that:

- Organophosphate poisoning presents with signs of muscarinic excess, such as **nausea**, **vomiting**, **excessive salivation**, **excessive perspiration**, **diarrhea**, **urinary urgency**, **bronchospasm**, and **flushing**
- **Miosis** (or even **pin-point pupils**) is a significant clinical sign of poisoning with cholinomimetics
- Severe poisoning can lead to **convulsions**, **coma**, and even **death**
- Similar signs can also be seen in poisoning due to certain mushrooms (e.g., genus Inocybe) containing muscarinic alkaloids. Signs of **mushroom poisoning** usually appear within 15-30 minutes of their consumption
- **Atropine** is the standard antidote
- **Topical pilocarpine** can cause **adverse effects,** like blurred vision, night blindness, and brow ache

Nicotine toxicity

Acute nicotine toxicity can occur due to the **ingestion of nicotine insecticides or tobacco**. Most of the nicotine in a cigarette is destroyed by burning or escapes via smoke, reducing the chances of nicotine poisoning among cigarette smokers.

Acute toxicity symptoms include **nausea**, **vomiting**, **hypertension**, **cardiac arrhythmias**, **central nervous system stimulation** (convulsions, coma, death due to respiratory arrest), **skeletal muscle end-plate depolarization blockade** (skeletal and respiratory muscle paralysis) and **symptoms of muscarinic excess** (due to parasympathetic ganglion stimulation). In acute poisoning, a fatal dose of nicotine is ~40 mg or 1 drop of pure liquid.

Treatment of acute nicotine toxicity is mainly symptomatic, such as **atropine** for symptoms of muscarinic excess, **diazepam** for central nervous system stimulation, and **mechanical ventilation** for neuromuscular paralysis.

Chronic nicotine toxicity in smokers is associated with increased risk of **vascular disease**, **coronary artery disease**, **sudden coronary death**, **peptic ulcer**, and **certain pulmonary diseases**. **Smoking cessation**, which requires counseling and motivation, is the most critical step.

For motivated patients, nicotine in forms with low abuse potential (such as gum, transdermal patch, nasal spray, and inhalers) can serve as **replacement therapy**. Slowly absorbed nicotine from these forms occupies the α4β2 receptors in the central nervous system and reduces craving.

Varenicline

Varenicline is a partial agonist at the α4β2 receptors. It is also effective for smoking cessation. However, patients must be monitored for potentially serious side effects, including **nausea**, **insomnia**, **exacerbated anxiety and depression,** and, possibly, **suicidal ideation**.

Muscarine Intoxication

Certain mushrooms are rich in muscarine, especially *Inocybe.* Muscarine intoxication symptoms typically appear within one-quarter to two hours of ingestion and include headache, nausea, vomiting, and constriction of the pharynx. Then salivation, lacrimation, and diffuse perspiration set in, combined with miosis, disturbed accommodation, and reduced vision.

Gastric and small bowel colic leads to diarrhea, and there is a painful urge to urinate. Bronchoconstriction leads to asthmatic attacks and severe dyspnea, and bradycardia, combined with marked hypotension and vasodilation, results in circulatory shock. Death after 8 to 9 hours occurs in about 5% of the cases, but this outcome **can be avoided with prompt diagnosis and treatment with atropine**.

Pilocarpine

Pilocarpine is a medication used to treat increased pressure inside the eye. In eye drop form, it is a treatment for angle-closure glaucoma until surgery can be performed, ocular hypertension, and open-angle glaucoma. Pilocarpine drops bring about constriction of the pupil following dilation. By mouth, it is used for the dry mouth resulting from Sjogren's syndrome or radiation therapy. The M_3 receptor is found on the iris sphincter muscle, where pilocarpine causes the muscle to contract (miosis). Pilocarpine also acts on the ciliary muscle and causes it to contract, which opens the trabecular meshwork. This action facilitates the drainage of aqueous humor to decrease intraocular pressure.

Another important use of Pilocarpine is for the diagnosis of cystic fibrosis by stimulating the sweat glands in the sweat test to measure the concentrations of chloride and sodium that are excreted in sweat.

Indirect-acting

Indirect-acting parasympathomimetic drugs may be either reversible cholinesterase inhibitors, irreversible cholinesterase inhibitors, drugs that promote ACh release, or anti-adrenergic drugs. The latter inhibits the antagonistic system, the sympathetic nervous system.

Reversible cholinesterase inhibitors	Irreversible cholinesterase inhibitors	ACh release promoters	Anti-adrenergics
• Donepezil • Edrophonium • Neostigmine • Physostigmine • Pyridostigmine • Rivastigmine • Tacrine • Caffeine (non-competitive) • Huperzine A	• Echothiophate • Isoflurophate • Malathion	• Cisapride • Domperidone • Metoclopramide • Risperidone • Paliperidone • Trazodone – via blockade of the α adrenergic receptors	Alpha-blockers: • Doxazosin • Tamsulosin • Prazosin • Phenoxybenzamine Beta-blockers: • Atenolol • Propranolol • Labetalol

Toxicity of Cholinesterase Inhibitors

Cholinesterase inhibitors (organophosphates and carbamates) are widely available as pesticides and veterinary vermifuges. **Acute or chronic exposure** can cause **poisoning** in humans.

Acute intoxication presents with signs of **muscarinic excess** (nausea, vomiting, excessive salivation, excessive perspiration, diarrhea, urinary urgency, bronchospasm, excessive tracheobronchial secretions, and miosis), **central nervous system signs** (cognitive disturbances, convulsions, or coma) and **peripheral nicotinic effects** (depolarizing neuromuscular blockade).

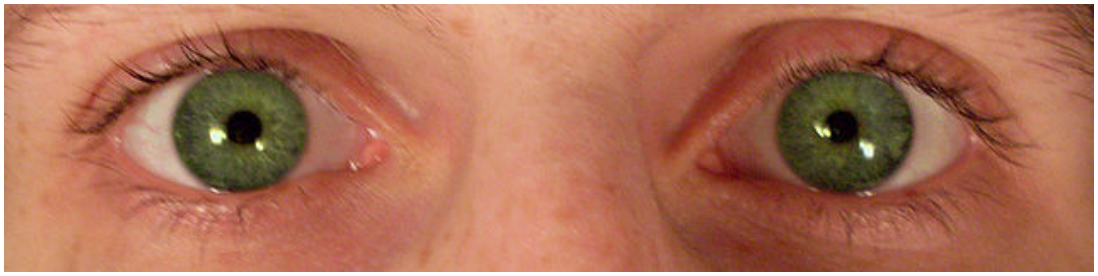

Image: “A 25 year old Caucasian male with miosis due to opiate (i.e., codeine) use.” by Anonymous. License: CC0 1.0

Central nervous system side effects are more common with physostigmine than with neostigmine or pyridostigmine because **physostigmine enters the CNS** while the others cannot.

Compared to direct-acting cholinomimetics, poisoning with cholinesterase inhibitors has the following differences: vasodilation is uncommon, and bradycardia is more common than tachycardia.

The most common organophosphate is malathion. **Malathion** is a cholinesterase inhibitor, a diverse family of chemicals that includes **sarin and carbaryl**. Carbaryl **enters the CNS,** where it irreversibly oxidizes acetylcholinesterase. All organophosphates interfere with the cholinergic nervous system and cause death. The effects of the neurotransmitter acetylcholine cannot be terminated by carbamoylated acetylcholinesterase. Upon uptake into the target organism, it binds irreversibly to several random serine residues on the cholinesterase enzyme, with peroxide as the leaving group.

The resultant phosphoester group is strongly bound to the cholinesterase and **irreversibly deactivates the enzyme,** which leads to a rapid build-up of acetylcholine

at the synapse.

Parathion is a cholinesterase inhibitor. It generally disrupts the nervous system by inhibiting acetylcholinesterase. Parathion acts on the enzyme acetylcholinesterase indirectly. After an insect (or a human) ingests parathion, an oxidase replaces the double-bonded sulfur with oxygen to give paraoxon. Parathion and related organophosphorus pesticides are used in hundreds of thousands of poisonings annually, especially suicides (it is known as *schwiegermuttergift*, or "mother-in-law poison," in Germany). For this reason, most formulations contain a blue dye as a warning.

Nerve toxicity can also develop 1-4 days after exposure to organophosphate insecticides, which is known as an intermediate syndrome. It is also characterized by muscular weakness; the toxicity mechanism seems to be related to cholinesterase inhibition, but this remains to be proven.

Since cholinesterase inhibitors are used as chemical weapons in war, soldiers and civilians are provided with autoinjection syringes containing carbamate, pyridostigmine, and atropine. **Pyridostigmine** prevents prolonged cholinesterase inhibition by impeding the binding of the chemical agent; however, it does not enter the central nervous system.

Tacrine, an anticholinesterase used to treat Alzheimer's disease, is replaced with other drugs due to its **hepatotoxicity**.

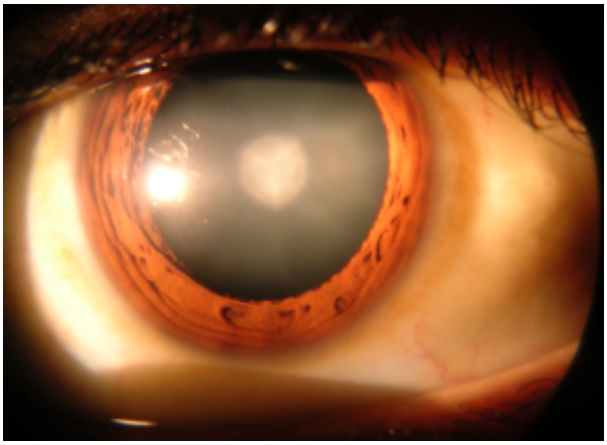

Image: "Cataract in the human eye" by Rakesh Ahuja, MD – Own work, License: CC BY-SA 3.0

The important adverse effects of **donepezil, rivastigmine, and galantamine,** which are anticholinesterase drugs used to treat Alzheimer's disease, is **gastrointestinal distress**.

Chronic exposure to **triorthocresyl phosphate**, which is used as an additive in lubricating oils, can cause delayed demyelinating neuropathy 1-2 weeks after exposure by inhibiting **neuropathy target esterase (NTE)**. Clinical presentation includes limb weakness and an unsteady gait.

Important adverse effects associated with **echothiophate** (previously used topically to treat glaucoma) are brow ache, uveitis, blurred vision, and cataract formation.

Treatment of Cholinomimetic Toxicity

Management of acute anticholinesterase poisoning

- Maintain vital signs, with particular attention to respiration
- Prevent further absorption of the agent (remove clothing and wash the skin if exposure is through the skin)
- Manage other symptoms (for example, control seizures with benzodiazepines)
- Specific antidotes: atropine & cholinesterase reactivators

Atropine

- Very useful for the treatment of **muscarinic symptoms**
- Higher doses are necessary to counteract central actions
- **Peripheral muscular paralysis cannot be reversed by atropine since it is a nicotinic effect**

Cholinesterase reactivators

Cholinesterase reactivators are composed of substituted oximes that regenerate active cholinesterase from the **organophosphorus-cholinesterase complex**. They attach to the anionic site of cholinesterase, which is unoccupied by organophosphates. **The anionic site is not free in case of carbamates**—cholinesterase reactivators are ineffective and contraindicated in carbamate poisoning because they also have weak anti-cholinesterase activity.

Cholinesterase reactivators are most effective when administered as early as possible before the phosphorylated cholinesterase has undergone aging.

Pralidoxime can reverse both muscarinic and nicotinic peripheral effects, but it cannot reverse CNS effects since it **cannot penetrate the CNS**.

Other important cholinesterase reactivators are **obidoxime** (more potent than pralidoxime) and **diacetyl-monoxime (DAM)** (a lipophilic cholinesterase reactivator).

Myasthenic Crisis versus Cholinergic Crisis

Myasthenic Crisis	Cholinergic Crisis
The pathophysiologic cause is insufficient cholinesterase inhibitors in the presence of fewer acetylcholine receptors	The pathophysiologic cause is excess of acetylcholine due to excessive cholinesterase inhibitors
External ophthalmoplegia present	External ophthalmoplegia absent
Pupils normal and reactive to light	Pupils reactive to light but miosis present
Ptosis usually present	Ptosis usually absent
Fasciculations absent in skeletal muscles	Fasciculations present in skeletal muscles
Increased blood pressure	Decreased blood pressure
Bowel and bladder incontinence	Abdominal cramps, nausea, vomiting, diarrhea
Edrophonium gives temporary relief	Edrophonium has no effect but may worsen symptoms
Atropine does not improve symptoms	Atropine improves symptoms

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Notes