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Chemical Emergency Medical Guideline

Information and recommendations for healthcare professionals

Cholinesterase inhibitors

CAS No.: 13071-79-9; 298-02-2; 60-51-5; 3383-96-8; 63-25-2

GHS symbols:

GHS06
Acute toxicity

GHS08
Health hazard

Signal word: Danger

Hazard statements:

For detailed information on the H statements for the individual substances within this group, it is recommended to consult the relevant safety data sheets provided by the distributor or official databases (e.g. https://echa.europa.eu/de/search-for-chemicals).

Overview

- Before the paramedic/emergency doctor approaches a patient, who has been or is exposed to a cholinesterase inhibitor, it must be ensured that there is no danger to themselves from this cholinesterase inhibitor.
- A patient whose clothing or vomit is contaminated with a cholinesterase inhibitor may endanger other people through direct contact.
- Poisoning with cholinesterase inhibitors can be fatal within minutes. If the presence of a cholinesterase inhibitor is suspected and various symptoms such as vomiting, diarrhea, excessive secretion, sweating, shortness of breath, tremors, weakness, headache, confusion or unconsciousness/coma are present, cholinesterase inhibitor poisoning should be assumed.
- If cholinesterase inhibitor poisoning is suspected, it is crucial to administer pure oxygen and secure the airways. The antidote atropine should be administered as soon as possible.
- The antidote atropine should be dosed according to the severity of the poisoning. In cases of organophosphate poisoning, enzyme reactivators such as pralidoxime or obidoxime may also be effective.

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1. Information on the substance

Cholinesterase inhibitors, e.g. terbufos (COUNTER), phorate (THIMET), dimethoate (CYGON), temephos (ABATE), carbaryl.
Synonyms: anti-cholinesterase pesticides, organophosphates and N-methylcarbamate insecticides.
These chemicals are currently the most widely used insecticides. They share the common mode of action of cholinesterase inhibition and can cause similar acute symptoms. However, the potency can vary greatly depending on the substance in question. There can also be significant differences in terms of their mode of action and treatment. It is therefore very important to identify the specific active ingredient or at least the respective class of active ingredients.

2. Exposition

2.1. Inhalation

Cholinesterase inhibitors are rapidly absorbed through the lungs.

2.2. Skin/eye contact

Cholinesterase inhibitors are absorbed through the skin and mucous membranes.

2.3. Ingestion

Cholinesterase inhibitors are absorbed in the gastrointestinal tract.

3. Acute health effects

Symptoms may occur within minutes or be delayed for up to 12 hours. While low exposure may cause biochemical effects without symptoms, mild poisoning usually causes a slight increase in secretions, such as saliva, tears, nasal secretions and mucus, with normal consciousness. Classic initial symptoms can be remembered with the acronym "SLUDGE": salivation, lacrimation, urination, diarrhea, gastrointestinal distress and emesis.

Other possible symptoms include nausea, sweating and chest tightness. A characteristic sign is a reduction in pupil size (miosis), but its absence does not rule out the diagnosis – especially in the early stages, pupil dilation may also occur. Severe poisoning is characterized by altered consciousness, heavy secretions and sweating ("everything is running"), abnormal pupil size, weakness, muscle twitching, chest pain and shortness of breath. Life-threatening poisoning is accompanied by coma, seizures, massive secretions, cyanosis, pulmonary edema and respiratory arrest. If treatment is not started in time, poisoning can lead to death.

Cholinesterase inhibitors alter neurotransmission at all cholinergic synapses and can cause symptoms at four functional receptors: muscarinic receptors, ganglionic nicotinic receptors, nicotinic receptors of the skeletal muscle and in the central nervous system.

In general, certain muscarinic symptoms occur first (see the SLUDGE acronym). Stimulation of the ganglia can cause sympathetic stimulation, which can alter the expected clinical picture of muscarinic activation.

The signs, symptoms and onset of poisoning vary depending on the age of the patient, the specific agent and the strength of exposure. The cholinesterase effect varies greatly between patients. If intoxication is suspected, treatment must be based on clinical signs and symptoms, especially if the patient's medical history and information on previous illnesses are available.

3.1. Effect on muscarinic receptors

Very small pupils, distorted/blurred vision, excessive salivation, lacrimation and nasal secretion, sweating and bronchial secretion, bronchoconstriction, nausea, vomiting, diarrhea, abdominal cramps, incontinence, low blood pressure and low heart rate.

3.2. Effect on ganglionic nicotinic receptors

High heart rate, high blood pressure and dilated pupils.

3.3. Effect on nicotinic receptors in skeletal muscle

Tremors, muscle twitching, cramps, weakness, flaccid tone, respiratory weakness.

3.4. Central nervous system

Dizziness, agitation, anxiety, sluggishness, headache, confusion, drowsiness, seizures, loss of consciousness.
Acute CNS effects are a typical sign of significant poisoning in adults and may dominate the clinical picture in children. Symptoms may include excitability, nervousness, dizziness, fatigue, lethargy, confusion, slurred speech, convulsions, loss of consciousness and respiratory depression.

3.5. Respiratory tract

Bronchoconstriction and significantly increased bronchial secretion may occur. Respiratory distress may result from central respiratory depression, paralysis of the respiratory muscles and progressive obstruction of the airways by bronchial secretions.

3.6. Skin/eye contact

Cholinesterase inhibitors are absorbed immediately and rapidly through the skin. Skin contact can have systemic effects. Local contamination of the eye always causes miosis. General poisoning can cause either mydriasis or miosis. Spasm of the ciliary muscle, which is important for accommodation, leads to distorted/blurred vision and pain in the eye. The hydrocarbon-containing solutions used in commercial pesticides can cause eye irritation.

3.7. Gastrointestinal tract

Nausea, vomiting, abdominal cramps, diarrhea and incontinence are common effects regardless of the route of exposure.

3.8. Acid-base status

Heavy sweating is likely and leads to severe dehydration.

3.9. Possible consequences

In uncomplicated cases, the patient should be completely symptom-free within 1-2 weeks. Complications may occur in the form of delayed neurological syndromes, aspiration pneumonia and respiratory failure in cases of pneumonia, sepsis or other problems associated with intensive care unit stay. Patients with prolonged hypoxia due to acute respiratory disorders may suffer damage to the brain or other organs.
Residual neuropsychiatric symptoms such as confusion, fatigue, excitability, nervousness and memory impairment may sometimes persist for several weeks. One to three weeks after acute exposure to organophosphate compounds, delayed neuropathy of a mixed sensorimotor type may develop.

4. Measures

4.1. Self-protection of first aiders

If there is suspicion that the area the helper must enter contains a cholinesterase inhibitor, direct contact with contaminated clothing, skin and vomit of the patient, as well as contaminated surfaces, must be avoided. Neoprene or nitrile gloves, rubber boots and chemical protection suits should be worn. Vinyl or leather gloves do not provide adequate protection.

Respiratory protection is necessary for first responders, as toxic effects can be caused by inhaling a cholinesterase inhibitor. Depending on the extent of the contamination, a self-contained breathing apparatus should be considered. A patient who is themselves or whose clothing is contaminated with chemicals containing a cholinesterase inhibitor may endanger other people through direct contact.
Note: The inner surfaces of gloves, boots and head protection may be contaminated, as may other items of equipment.

4.2. Rescue

Patients should be removed from the danger zone immediately. If they are unable to walk unaided, they should be removed from the danger zone quickly using appropriate means, taking care to protect yourself. The "A, B, C procedure" then takes absolute priority.

A) Clear the airways (check for blockages caused by the tongue or foreign objects)
B) Ventilation (check the patient's breathing, if necessary, begin ventilation with adequate self-protection, e.g. breathing mask)
C) Circulation (begin resuscitation for any person who does not respond to verbal commands and is not breathing normally)

"CRASH" decontamination

- Rescue patients contaminated with hydrofluoric acid who are unconscious or unable to move (critically ill or injured patients according to the ABCDE scheme) from the immediate danger zone, taking care to protect yourself with suitable personal protective equipment.
- If necessary, perform emergency measures ("basic life support"; e.g. bleeding control using a tourniquet, chest compressions, etc.)
- At a suitable location outside the danger zone, completely undress the contaminated patient using an emergency rescue knife, taking care to protect yourself (duration: approx. 1 minute).
- Shower/rinse with plenty of water (duration: approx. 1 minute).
- Transfer to a clean stretcher. Ensure body heat is maintained.
- Transport/handover to the emergency services/emergency doctor (duration: approx. 1 minute)

4.3. Cleaning

Patients suspected of having been in contact with chemicals containing cholinesterase inhibitors require cleaning measures. If possible, patients should assist with their own cleaning. Contaminated clothing should be removed as quickly as possible and securely packed (plastic bag), while affected skin and hair areas should be rinsed with water for 15 minutes. Then further clean the skin and hair areas with soap or a mild liquid detergent and water. The patient's eyes should be protected during the cleaning of the skin and hair areas.
Contaminated clothing should be washed separately before further use. Contaminated leather items such as shoes, belts or wallets must be disposed of.
Exposed or irritated eyes should be rinsed with water or neutral saline solution for 15 minutes. Contact lenses should be removed, if possible, without additional risk to the eye.

4.4. Antidote treatment

Patients with known or highly probable poisoning with a cholinesterase inhibitor should be treated with antidotes as follows by emergency medical services. The availability of antidotes may vary from country to country due to legal regulations or ordinances.

Atropine should be administered intravenously (IV). Depending on the severity of the poisoning, adults should be given an initial dose of 1-2mg IV (or 0.05mg/kg body weight for children under 12 years of age), followed by repeated doses every 15 minutes until excessive secretion and sweat production are under control. If the diagnosis is confirmed but there is no response to treatment, an increase in the dose should be considered. Atropine is not effective against nicotinic effects, in particular muscle weakness, muscle twitching and respiratory depression.

At the same time, cleaning should be continued with appropriate protective clothing. Further doses of atropine should be administered depending on the recurrence of symptoms. In cases of severe organophosphate poisoning, an initial bolus of 50mg may be necessary, followed by continuous infusion of 0.5–2.0mg/h for several days.

Carbamate poisoning usually requires much lower doses of atropine over a shorter period. The use of opiates, parasympathomimetic, theophylline, reserpine and phenothiazine should be avoided if possible. Adrenergic amines should only be administered for specific indications, such as low blood pressure.

In patients with significant impairment of the central nervous system and/or skeletal muscle function, which is very likely to have been caused by organophosphate poisoning, the administration of an acetylcholinesterase enzyme reactivator (e.g. obidoxime or pralidoxime) together with atropine may be considered. The best effect is achieved when this reactivator is administered as soon as possible after intoxication.
Note: Enzymatic cleavage of an alkyl residue of the phosphate residue occurs at the phosphorylated esterase ("ageing").

Before administering an enzyme reactivator, blood samples should be taken for standard determination of serum parameters and erythrocyte cholinesterase activity. Obidoxime/pralidoxime can be given as a continuous infusion after a loading dose or as a slowly administered bolus, adjusted for age and weight if necessary. The recommended dose for obidoxime is 250mg intravenously, followed by 750mg/day as a continuous infusion (pralidoxime: 1.0-2.0g intravenous infusion in patients older than 12 years, but no more than 0.2g/minute).

Diethyl organophosphates (e.g. parathion, phoxin, pyrazophos) are associated with slow esterase "ageing" (see above), while dimethyl organophosphates (e.g. dimethoate, omethoate, phosphamidone) are associated with rapid esterase "ageing". In the first group of compounds, the administration of oximes is generally beneficial, whereas in the second group, oximes can only reactivate the enzymes or prolong the ageing process if they are administered promptly after exposure.

In the event of neurological seizures following atropine/oxime therapy, a benzodiazepine, e.g. diazepam, should be administered intravenously. If the seizures persist or recur, phenobarbital should be administered, followed by phenytoin if necessary. Furosemide may be given to treat pulmonary oedema if rattling sounds can be heard in the lungs even after maximum doses of atropine have been administered.

All symptomatic patients who have been exposed to high concentrations of a cholinesterase inhibitor and require treatment with atropine should be transported to a hospital with intensive care facilities. After administration of atropine has been completed, the patient should remain under constant observation – for at least 72 hours in the case of organophosphates and for at least 24 hours in the case of carbamate poisoning.

Further exposure to cholinesterase inhibitors must be prevented until laboratory tests confirm that cholinesterase levels have sufficiently recovered.

4.5. Initial treatment (preclinical or clinical)

Speed is crucial. If the patient shows signs of poisoning, the airways should be secured and 100% oxygen administered. Atropine should be used as an antidote. With a good oxygen supply, the risk of arrhythmia associated with the administration of atropine is minimized. In cases of severe poisoning, treatment should be carried out simultaneously with decontamination.

Do not induce vomiting after ingestion.
Vomit and oral secretions should be removed by suction to prevent aspiration; direct contact with contaminated fluids must be avoided at all costs. It should be noted that intubation, suction and other manipulation of the head and neck prior to administration of atropine may cause bradycardia.

Immediate gastric lavage should only be considered if a life-threatening dose has been swallowed less than 60 minutes ago.

Patients who are conscious and able to swallow should receive 50 g of activated charcoal (or 1 g/kg body weight for children weighing up to 50 kg) within two hours of exposure. Repeated administration of activated charcoal is possible at any time to complete decontamination if there are signs or suspicion of ongoing absorption.
For multiple doses, start with the single-dose amount mentioned above, followed by the same dose every four hours or half the dose every two hours. Avoid inhaling the product.

However, if significant amounts of a cholinesterase inhibitor have been ingested, diarrhea and/or vomiting are so likely that neither activated charcoal nor laxative is indicated. Gastric lavage fluid and vomiting must be isolated and disposed of safely.

4.6. Further procedure and treatment

In addition to taking a medical history, performing a physical examination and monitoring vital signs, pulse oximetry and a chest X-ray should be performed.
Continuous ECG monitoring and regular checks of electrolyte levels, especially potassium, are recommended in all cases treated with atropine.

It is not clinically proven whether hemoperfusion, hemodialysis or exchange transfusion influence the severity or duration of poisoning.

4.7. Laboratory tests

The diagnosis of acute toxic effects of cholinesterase inhibitors is primarily a clinical diagnosis based on the rapid onset of characteristic symptoms such as increased secretion, muscle twitching and weakness, and changes in consciousness, particularly when there is a high degree of suspicion of exposure to cholinesterase inhibitors.

If there are clear clinical indications of acute poisoning by a cholinesterase inhibitor, the patient should be treated immediately, even without precise knowledge of the exact substance and exposure dose. Under no circumstances should laboratory confirmation of poisoning be awaited.

If the patient's condition is not due to cholinesterase inhibition, the patient will develop signs of anticholinergic syndrome (tachycardia, tachypnoea, mydriasis, dry skin, etc.) after receiving the first dose of atropine. In this case, the possible differential diagnoses must then be determined.

The toxic effects of a cholinesterase inhibitor from the organophosphate class can be determined in the laboratory by measuring plasma pseudocholinesterase and erythrocyte acetylcholinesterase.
Unless a considerable amount of N-methylcarbamate has been ingested and a blood sample taken within 1-2 hours, laboratory detection of reduced cholinesterase activity in the blood is unlikely.

Routine laboratory tests include a complete blood count, glucose, amylase and electrolyte determinations. A urine sample (or vomiting, if the agent has been swallowed) should be collected for analysis of metabolites.

In cases of severe poisoning, arterial blood gases should be determined to assess oxygenation and acid-base status. Metabolic acidosis should be corrected with bicarbonate if the blood pH falls below 7.15. Electrolyte disturbances (e.g. hyperkaliemia) should also be evaluated and treated if necessary.

4.8. Discharge of the patient / instructions for further rules of conduct

Clinically asymptomatic patients who have only been exposed to cholinesterase inhibitors to a minor extent (depending on the duration of exposure), have not ingested any cholinesterase inhibitors and show no abnormal clinical findings and no signs of toxic effects of cholinesterase inhibitors after an appropriate follow-up period may be discharged under the following circumstances:

- Information and recommendations for patients with instructions for further action have been provided verbally and in writing. The patient has been instructed to seek immediate medical attention if any health problems arise.
- The patient is aware of and has understood the toxic effects of cholinesterase inhibitors and the

instructions for further action.

- The attending physician has been informed that regular contact between the patient and the physician is possible in the following 24 hours.
- Heavy physical work should not be done in the following 24 hours.

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