

Bioterrorism and Chemical Agents Part 1

Notes for slides

Chemical Agents

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Toxicology definitions

LD50 is the dose that is lethal to 50% of the population.

ID50 is the dose that is incapacitating to 50% of the population.

LC50 is the concentration in air in a given period of time (usually one hour) that will kill 50% of the test animals.

Ct is an estimate of dose. C is the concentration of vapor in air expressed as mg/m³ and t represents time. Thus the Ct is the product of the concentration per time. It does not indicate how much is retained or inhaled however.

LCt50 is defined as the concentration of vapor per unit of time that is lethal to 50% of the population.

Haber's law states that the Ct to produce a given biological effect is usually constant over an interval of several minutes to several hours. As an example., an effect produced by 0.05mg/m³ for 100 minutes is also produced by 5mg /m³ for 1 minute. The Ct is 5mg.min/m³ in both cases. This is a way of discussing the dose response curve.

Toxic chemicals can produce either a local or a systemic effect. Some local agents can later develop systemic effects.

There are three routes of exposure and many agents have different symptoms dependant upon the exposure route. They are oral, inhalational and cutaneous. Some agents have more than one route of entry at the time of exposure.

Factors related to toxicity:

1. Factors related to the chemical. Composition, physical characteristics, presence of impurities or breakdown products.
2. Factors related to the exposure. Dose concentration, route of exposure, duration
3. Factors related to the person exposed. Heredity, immune status, nutritional status, hormones, age, sex, health status.
4. Factors related to the environment. Media (air, water or soil), additional chemicals present, temperature, air pressure.

The LCt50 for tabun is 400 mg.min/m³, for sarin vapor it is 100 mg.min/m³, for soman is 50 mg.min/m³ and for VX it is 10 mg.min/m³.

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The first rule in a military setting is to hold your breath, put on your gas mask and inject with one or more MARK1 kits either by yourself or your buddy. Nerve gas vapor can kill after you inhale only one or two breaths of it. Once masked (with an M40 or M17A2 respirator), immediate detoxification is important. In the military, self decontamination is taught as a vital second step along with giving the atropine. An M291 kit contains charcoal and sorptive resins and the M258A1 kit contain absorptive material in the form of two towelettes. One is for G agents and the other for VX.

After a few minutes, a nerve agent penetrates the skin (10-20 minutes at most) and only the liquid type of agent, which is more persistent but still subject to evaporation, will need to be decontaminated. Skin decontamination is not required after nerve gas vapor exposure. Remove their clothes, which may be contaminated. With liquid agents after you remove their garments, wash them down with Clorox diluted 1 to 10. Scrape any thick material off and place it in a sealed bag. Make sure the hair is washed. Wash the Clorox off with running water to complete detoxification. If adsorbents are not available flour or tissue paper may help absorb some of the material.

Protect yourself or you may be a casualty. If is a liquid agent, such as VX, make sure you are adequately protected if you have the potential to be exposed to the agent. MOPP 4 or Level A protection is required. If it is a non-persistent vapor, a respirator and butyl or Neoprene gloves are required. In the medical setting you usually do not have the opportunity to help those exposed to the highest concentration of the gas or liquid. They will fatalities unless they are in a military setting and well trained and equipped to help themselves or their buddy. Thus you will be seeing individuals with a lesser amount of exposure. They may divided into mild , moderate and severe signs and symptoms (see slide) Decide if further treatment is required and if you are seeing them early or late after exposure. If they seem to be getting worse give Atropine and 2-PAM. In the military, there are three MARK I kits each containing 2 mg of atropine. Current military policy is to give all three followed by an autoinjector with 10 mg of Valium. The 2-Pam is given if clinical symptoms develop on a prn basis.

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None of these agents is a truly specific antidote but the atropine acts by blocking the effects of the excess acetylcholine at muscarinic receptor sites. This agent does not block the effect of the nerve agent as it binds to the acetylcholinesterase.

The 2-PAM (pyridine -2- aldoxime chloride) helps to reactivate the organophosphate inhibited cholinesterase. In the civilian sector it is best to give one vial (1 gram) of Protopam (Wyeth-Ayerst), which is 2 PAM Cl, IV over a 15 to 20 period of time. Hypertension will result which lasts several hours. It will help the fasciculations (nicotinic effect) but do not give too often. No more than 2.5 g for the first 1.5 hours.

If the organophosphate ChE complex ages or becomes fixed, then oximes will not work. Soman fixes rapidly so that drug therapy is relatively ineffective for this agent. Physostigmine used preventively is the best treatment for agents that fix rapidly. Physostigmine is a carbamate that reversibly attaches to the ChE receptor and acts as a competitive inhibitor for GD. Sarin takes about 5 hours to fix. Tabun is longer. VX does not age.

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There are three cholinesterases in the human body. (a) Tissue cholinesterases, which cannot be readily, measured, (b) butyrylcholinesterase (BuChE). BuChE is present both in tissue and blood. It is produced in liver with a replacement time of about 50 day. (c) RBC cholinesterase (RBC-ChE). BuChE is relevant because it is sometimes found to be low or abnormal in the population and if so will adversely influence individuals receiving succinylcholine with anesthesia causing prolonged paralysis. About 0.3% of the population is homozygous for low BuChE activity.

Since RBC-ChE levels are more stable than BuChE this test is considered more reliable and is used to monitor a organophosphate poisoning. The RBC has a life of 120 days. Recovery after a poisoning occurs only with production of new RBCs –about 1% per day. The blood ChE will be inhibited before the tissue ChE. Though BuChE activity is significantly more affected than RBC-ChE by such common insecticides as malathion and parathion, nerve gases cause the reverse with RBC-ChE rapidly reversed. A secondary pathway that is polymorphic is a two phase breakdown involving the cytochrome oxidase system followed by tissue and serum paroxonases is present for organophosphates and is also interfered with by these agents.

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At ground zero.

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Blister gases are HD for sulfur mustard, H for impure sulfur mustard, which originally stood for Hun. HN1, HN2, HN3 were discovered after the war by substituting nitrogen for the sulfur. HN3 is in some nations chemical inventory as a vesicant and respiratory irritant. HN2 later became known as Mustargen and was used as a mainstay for early cancer treatment as it is an alkylating agent. CX is Phosgene Oxime, an immediate reacting vesicant and L is Lewisite, which contains arsenic instead of sulfur.

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HD is 2,2 di(chloroethyl) sulfide. In high dose it can be lethal however in 85% of cases it produces prolonged morbidity, not mortality. It would easily tie up a civilian hospital group if a large amount of casualties occurred from this agent.

The only military casualty in the Gulf War was burned by HD in a captured bunker. He was left with some scars. No actual mustard was used on U.S. troops in that war but we know that Sadam

had deployed this agent in the front line. The Iraqis used this agent against Iran in their 1982-85 war and also on their own Kurdish citizens.

It is estimated that 17 nations have this type of chemical agent.

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The gas is really a oily liquid that vaporizes easily.. It is colorless and odorless in the pure state but in the impure state on the battlefield, it appeared brown to yellowish with a smell of garlic. It vaporized with increasing temperature so the Germans (and later the Allies) would deploy it at night and the thick vapor would roll with the prevailing wind low to the ground and drop into the trenches. The troops would expect that it was all right to remove their gas masks hours later when daylight occurred. As the temperature increased so did the volatility of Mustard so that those troops without a gas mask were poisoned. It readily penetrates clothing and the gas masks of those days did not offer much protection.

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With modest exposure after a latent period of at least 2 hours, the eyelids would swell and close, more conjunctival and corneal swelling and temporary blindness would occur though permanent blindness with mustard is uncommon. Upper respiratory symptoms begin with hoarseness leading to aphonia. There may be actual vocal cord damage. Rhinorrhea occurs with thick discharge and chest pain, bronchitis with increasingly abnormal pulmonary function tests noted. Late pulmonary effects continue to plague many Mustard survivors and there were continuing deaths in the 1920s, will after the war ended from emphysema and bronchitis symptoms, recurrent respiratory infections including pneumonia. In moderate doses frank blisters form on the skin. The blisters are not tender, they are thin walled and the fluid is not toxic. With higher amounts of agent or direct liquid contact the blisters may become necrotic. Pigmentation of the skin is common after Mustard burns even if vesicles don't form.

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Gassed by John singer Sargent. The bandages over their eyes indicate that they were gassed by Mustard.

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Provide general supportive care. It is possible for the physician to become poisoned by the patient so follow level A regulations as published in Managing Hazardous Materials Incidents as published by the Department of HHS, ATSDR. This can be obtained free. It will direct you in how to set up the emergency room, how to protect yourself and how to detoxify and protect the patient. Various military sources are available as well. There is no specific antidote to this compound.

The same treatment principles apply to the nitrogen mustards that are reviewed for sulphur or sulfur mustard.

Nontoxic pulmonary edema is treated aggressively with oxygen, PEEP or intubation and ventilation. Steroids are often used but may have little effect. Anorexia, fever depression, malaise occur as systemic effects.

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Lewisite is a dark brown liquid in the preparation used in munitions. It smells like geraniums but is instantly very irritating to the eyes, skin and respiratory tract. It is 2-chlorovinyl dichloroarsine. With strong alkalis it becomes a non-vesicant. It is soluble in solvents and hydrolyzes rapidly.

It is stored at only one facility at Toole Army Depot in Utah and is or has been slated for destruction by treaty. There is a delay at destroying our stockpile of chemical weapons as mandated by Presidential order in 1969.

It can produce systemic effects as it contains arsenic and interferes with lipoic acid, sulfhydryl radicals and other enzyme systems. These effects are usually not as significant as the burning eye and skin pathology or the severe respiratory symptoms. The blisters start in about 1 to 2 hours last about 72 hours.

In more severe cases, besides pulmonary edema, severe bronchial damage may occur, capillary leakage with anasarca leading to hypovolemia and renal compromise.

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Lewisite was named after Capt. W .L .Lewis who led an Allied team who synthesized it in 1918. It was not used in the war. British–Anti Lewisite (BAL) can be made in topical ointments, dilute eye drops, and given systemically at 3 mg deep IM, of the 10% in oil solution, every 4 hours for 2 days. 50% of recipients get sick from the BAL but the treatment is not worse than the disease. Newer agents such as meso-dimercaptosuccinic acid (DMSA) or dimercapto-1-propanesulfonate (DMPS) are more efficient in removing arsenic, safer, and can reduce the intracerebral arsenic level whereas BAL causes it to rise.

Detoxification can be carried out with a 10% sodium carbonate solution since the agent is neutralized by alkaline material. Follow this in 5 minutes with soap and water.

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One drop of this agent on the eye will cause coagulation necrosis with penetration of the cornea. One drop on the skin will cause it to turn white from immediate coagulation necrosis. There is no battlefield use of this agent that I am aware of. There is no specific antidote. Treat the eye as a corrosive injury, treat the lungs as you do for a toxic or noncardiac pulmonary edema. In decontaminating this agent, use sodium bicarbonate and not a chlorinating agent.

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Cyanides have been used extensively in this country for manufacturing purposes. It is used in electroplating, gold and silver processing, tanning, metallurgy, chemical processing and other compounds. It has been used in executions, suicides and poisonings for many years. Cyanide poisoning has been reported from eating chokecherries, bitter almonds and apricot pits. It is a component of Laetrile. Cassava, a staple, is blamed for a high incidence of tropical ataxic neuropathy due to its amount of cyanide. Cigarette smoke contains cyanide so that the smoker has about 17 µg/mL. (Controls average about 0.06 µg/mL.) The gas chamber utilizes the principle of generating Hydrogen Cyanide (HCN). Dropping a cyanide salt into a strong acid produces it. Numerous international terror attempts have used HCN release. Most recently the Aum Shinrikyo cult used cyanide salt and acid in restrooms in the Tokyo subway several weeks after the sarin nerve gas attacks in March 1995.

Cyanogen chloride has a strong pungent odor. It does not dissolve in water well but does in organic solvents. It vapor is heavier than air (2.10 vapor density) and unlike hydrogen cyanide, it is very irritating to the eyes and mucous membranes and can produce pulmonary edema. This compound is usually non-persistent. CK's boiling point is 12.9 C, vapor pressure is 1,010 mg Hg, and in a pure form it is a colorless gas or liquid. The LCt is 11,000 mg.min/m³.

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If symptoms are mild. one may defer the treatment since there is some risk with producing methemoglobin.

Other clues to cyanide poisoning are a cherry red skin coloration since it causes a peripheral vasodilation, and a burnt almond smell, which is only detectable to portion of individuals due to genetic traits. Blood cyanide levels must be performed on whole blood since most of the cyanide is rapidly within the red blood cell. It tends to fall in stored samples due to its short half life. Levels of 0.5 to 1.0 mgm/mL are associated with early symptoms. Levels of 2.5 to 3 mg/mL are associated with coma and levels over 3 are associated with death. One will not have the luxury of a cyanide level to make the diagnosis however and must rely on clinical circumstances.

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First you must rapidly bind or fixate the cyanide ion either by creating methemoglobin or fixing it with cobalt compounds. Any person who is conscious and breathing normally more than 5 minutes after being exposed to and removed from cyanide agents will recover without any treatment

as this substance is rapidly detoxified by the body. In those with symptoms, remove the patient from the source while wearing PPE. There are four methods used to fixate cyanide.

(a) Amyl nitrite is often used if there is a respiratory positive pressure present. Do not use amyl nitrate with oxygen as an explosion may occur. Follow this with sodium thiosulphate. In the military amyl nitrate is used less than in the civilian sector. More meaningful and predictable levels of methemoglobin can be produced by the latter.

If there is impairment with breathing, IV sodium nitrate should be used (10 cc of a 3% solution, 300mg over 3 minutes). This will produce methemoglobin, which binds the cyanide. Keep the patient flat or their blood pressure will fall from the nitrite. Try to obtain a little cyanosis to indicate methemoglobinemia

A newer agent, 4-Dimethylaminophenol-hydrochloride (DMAP), is very effective in treating cyanide poisoning. If available, give it instead of the nitrites at a dose of 250 Mg IV slowly every hour until sodium thiosulphate is made available. The dose must be adjusted for children. Administer the sodium thiosulphate at a dose of 12.5 Gms (50 cc of a 50% solution over a 10 minute period of time.) The DMAP can be stopped once the sodium thiosulphate is given. This used by the German military and 3 mg/kg IV can produce a methemoglobin level of 15% in one minute. Disadvantages of 4-DMAP are necrosis in the area if given IM, increases in pain, fever and elevated muscle enzymes can be seen. Very high levels of methemoglobin are undesirable.

Another alternative way to initially bind cyanide is with intravenous hydroxycyanocobalamine. This is commercially available but large amounts (4 g) IV slowly should be used as compared to the IM route. The cobalt will act to bind a portion of the cyanide and complex it until the thiosulphate is employed to finish the job. HydroxyB12 is relatively safe. Disadvantages include rare allergic reaction, high cost for the amounts required, short half-life as it decomposes in light.

Remember that sodium thiosulphate must always be given to complete the medical detoxification of cyanate by converting the free and bound cyanide to thiocyanates under the influence of the enzyme rhodenase. The relatively nontoxic thiocyanates can be metabolized.

There are four methods in the human to detoxify cyanide. The most effective of these is via rhodenase but it is rate limited by a rapid decline in sulfur containing substrate. Thiocyanate is the natural product of this process. The addition of more thiocyanate helps improve this process by adding sulfur molecules.

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