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Review Article

Chemical warfare agents and treatment strategies

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Abstract

Chemical agents; is the general name of substances known to have toxic effects on the environment, which cause a large number of deaths and disabilities in a short period of time. These agents are divided into subclasses such as blister, nerve, choking, incapacitating/behavior altering, and asphyxiants/blood agents. In addition to the short-term effects of these agents there may be long-term reflections which affect the next generation. The previous century has been an important period in terms of observing the problems arising from the usage of the agents during wars. Deaths only due to nerve agents are thought to exceed 5 millions in recent wars. Especially the situation that the World War II has emerged shows the magnitude of the use of chemical agents. Due to these detrimental effects, their usage is restricted or prohibited by various international organizations. Despite these obstacles, chemical agents have been used by some countries and terrorist groups. Effects of these agents can take part vary from basic symptoms such as nose irritation to serious problems such as respiratory arrest. Healthcare professionals working in the management of exposure to these agents should have sufficient knowledge and be aware of their effects on the body. For this purpose; we discussed the serious effects of chemical warfare agents on human health and environment, post-exposure applications and pharmacological treatment options.

Keywords: Chemical Warfare Agents; Gas Poisoning; Decontamination; Drug Therapy.

Chemical warfare is a type of warfare which is done by using chemical agents. Chemical warfare agents are incapatitating, damaging, toxic and lethal compounds. It is known that; chemical warfare agents have been used since 600 B.C. Even though these agents have been used many times intermittently (Figure 1), their use increased significantly in the course of World War I (WWI) (1). Cyanide, phosgene, chlorine, sulphur mustard etc., were weaponized in WWI (2,3).

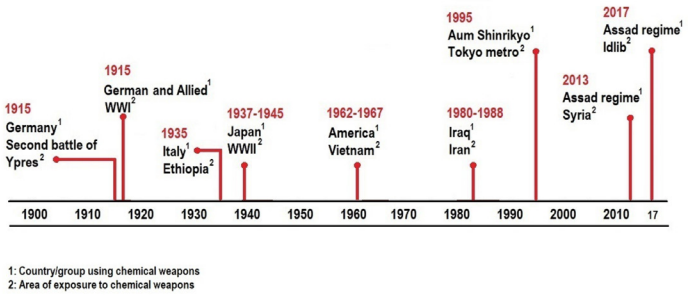

Figure 1. These agents have been used in different places and times so far, as shown above. Adapted from Syria's latest atrocity: Assad kills at least 85 with chemical weapons, In The Economist, Retrieved August 10, 2018, from https://www.economist.com/middle-east-and-africa/2017/04/08/assad-kills-at-least-85-with-chemical-weapons. Copyright 2017.

Clorine was used by Germany in 1915. Nearly 10,000 people died and over a million people got injured. Therefore in the late 1930s Germany discovered the sarin and tabun. Japan and Germany used chemical weapon against China and Jews, respectively in WWII. After WWII, Iraq used nerve agents and mustard against Iran in Gulf War (1980-1988). Syria has been exposed to chemical attacks since 2012. It is estimated that there were utilization of chemical weapons in recent attack on April 7, 2018 against civilians in Douma city, East Ghouta and Syria (4). There were over the 40 deaths as a result of this suspicious chemical attack. It is being investigated whether toxic gases were used or not in this attack (5).

Chemical warfare agents are cheap and toxic compounds which are produced and stored easily. Hence, they may be utilized as weapon. While their use is controlled by Organisation for the Prohibition of Chemical Weapons (OPCW) and Chemical Weapons Convention (CWC), some countries and terrorist groups disobey the prohibition. In addition, some chemicals are used in industry. Therefore, their manufacture can not be banned (2,3). To summarize,

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chemical agents continue to threaten public health and safety.

Chemical warfare agents have been classified qua blister, nerve, choking, incapacitating/behavior altering, and asphyxiants/blood agents by North Atlantic Treaty Organization (NATO) (Table 1). It can be done many different classification based on toxicity mechanisms, target organ, clinical fetaures and etc. (2,3). We used classification of NATO in this review.

Table 1. Classification of the most known chemical warfare agents

Blister agents	Nerve agents	Choking agents	Asphyxiants/ Blood agents	Behavioural agents/ Incapatitating
Sulfur mustard	G Series	Phosgene	Hydrogen cyanide	Lysergic acid Diethylamide (LSD-25)
Nitrogen mustard	• Sarin	Diphosgene	Cyanogen chloride	Ketamine
Lewisite	• Soman	Chlorine	Arsine	
	• Tabun	Chloropicrin		
	V Series			

Blister Agents

Blister agents involve mustard agents (sulfur mustard and nitrogen mustard) and lewisite; their chemical formulas are 2,2'-dichlorethyl sulfide, bis (2-chloroethyl) methylamine and 2-chloroethenylarsonous dichloride, respectively. When the skin is exposed to these agents, vesicles form on the skin (2). In addition to the skin, blister agents especially affect the eyes and airway with airborne exposure (6).

Mustard agents are classified as sulfur mustard and nitrogen mustard. Sulfur mustard is pale yellow, oily liquid and smells like mustard. It volatilizes at 25 ^{0}C and is fractionated at 217,5 ^{0}C. It dissolves in water, fat and fat solvents. Also, clothes do not protect from aerosols. Sulfur mustard is not used in the industry. Nitrogen mustard has a weak odor, it smells like fish or mildew. It dissolves slightly in water however, it dissolves well in organic substances such as acetone. Nitrogen mustard is fractionated at temperatures above 194 ^{0}C and it is not used in the industry. It is known that nitrogen mustard was produced in 1920s and 1930s for use qua a chemical weapon. During WWII it was produced by United States (U.S.) and Germany, but was not utilized (2).

Sulfur mustard and nitrogen mustard have similar mechanism of action and they lead to similar signs and symptoms as a result of their exposure. Mustard agents may cause conjunctivitis, photophobia, blepharospasm, pain, corneal damage when they contact with eyes. On the long view, eye damage may lead to glaucoma and may be irreversible. Mustard agents also may cause airway damage and pain sensation when they are inhaled (6). Namely, they bind to transient receptor potential (TRP) receptors. They consist of six transmembrane parts, are expressed in sensory nerve terminals (C fibers). Subsequently, they flow into the cell through TRP-channel. Immunmediators such as tachykinins, growth factors, bradykinin and immune modulators are released from the nerve terminal into the neighbouring area. These lead to migration of immune cells to the area and neurogenic inflammation. As a result of neurogenic inflammation, bronchial constriction, extravasation, alveolar damage apoptosis and pulmoner edema may occur. In addition, C fibers are excitated and release substance P. As a consequently, pain-signal is sent to brain via spinal cord. It is known that sulfur mustard activates TRPA1 receptor. TRPA1 and TRPV1 are co-expressed in airway sensory nerve endings. It is stated that TRPA1 ve TRPV1 reseptors' functions depend on each other (6,7).

Mustard agents are alkylating agents. Hence, they establish covalent bonds with many targets such as glutathione, guanine and fatty acides (8). If they bind to guanine, DNA breaks and crosslinks may occur and these events may lead to apoptosis of the cell. Their binding to fatty acides may result in membran damage. They can lead to bone marrow suppression as a systemic effect. Because of exposure to these agents leukocytes invade into the tissue, mast cells become active and inflammatory mediators (histamine, prostaglandins and cytokines etc.) are released. Thus, itching, erythema and edema arise. Due to the same mechanisms, epidermal thickness increases, epidermis and dermis are separated from each other. These effects arise 2-12 hours after sulfur mustard exposure whereas nitrogen mustard occurs these effects earlier than sulfur mustard. When sulfur mustard is inhaled; nasal irritation, nosebleed, laryngeal inflammation, voice changes, cough and dyspnea are occur. Airway necrosis with hemorrhagic edema, pseudomembrane formation and bronchial obstruction may occur and these may lead to decease within the day of exposure. Bacterial pneumonia added to this condition may lead to death in 3th-5th day of exposure. As a result of systemic absorption via ingestion, gastrointestinal symptoms such as nausea and vomiting, central nervous system symptoms such as seizures, behavioral abnormalities and psychological problems may be observed. Sulfur mustard exposure may cause delayed complications such as corneal inflammation, bronchial inflammation, lung fibrosis, increase/decrease of skin pigmentation and psychologic issues. Mohammad and his colleagues reported that 500 soldiers who were affected by sulfur mustard in course of war between Iran and Iraq in 1980s have pulmonary or eye problems 15 years after the war (2,6).

Lewisite is a arsenic-based, lipophilic, colorless and odorless liquid (9). It melts at -18 ^{0}C and boils at 190 ^{0}C. Its density is 1.89 g/cm^{3}. Lewisite hydrolyses in acidic medium. Thus, it forms hydrochloric acid (HCl) and chlorovinylarsenous oxide. Chlorovinylarsenous oxide is a compound which has a less-potent blistering effect than lewisite (10). Trisodium arsenate which is a toxic compound may occur when lewisite is exposed to alkaline solutions. It is not used in the industry. It is estimated that the LD50 (lethal dose, 50%) of lewisite is 30 mg/kg and LC50 (lethal concentration, 50%) of lewisite is 100.000 mg min/mm^{3} for dermatologic problems (2). Lewisite was discovered during WWI. It has not been used in any warfare. Because, it hydrolyses in water and the desired

effect can not be achieved in humid weather conditions. It is not used in industry. Lewisite is an agent which can penetrate ordinary clothes and rubber. Lewisite, a lipotropic agent, can be easily adsorbed via derm and its systemic absorption may be lethal. Lewisite's major target organs are skin, eyes and airways. It causes burning sensation, painful erythematous inflammation and blisters on the skin. Clinical features of lewisite exposure are similar to other blister agents. Lewisite do not cause bone marrow supression. Since lewisite is an arsenic-based agent, some signs and symptoms of arsenic toxicity may occur. It is estimated that lewisite is more reactive agent than mustard agents. Lewisite leads to inhibit pyruvate dehydrogenase by binding to the two tiol groups of lipoic acid. Pyruvate dehydrogenase is an enzyme which converts pyruvate to acetyl coenzyme A. Thus, lewisite causes deterioration in oxidative phosphorylation. It also may lead to oxidative stress, DNA adducts and apoptosis. Lewisite also damages capillary walls, it causes hypovolemia and refractory hypotension. This phenomenon is called 'lewisite shock' and causes death (2,6,9).

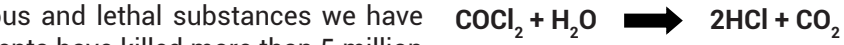
Nerve Agents

Nerve gasses are phosphorus compounds which inhibit the acetylcholinesterase enzyme (AChE). These agents are the most dangerous and lethal substances we have ever known. These agents have killed more than 5 million people in recent wars (11,12). These agents are divided into subclasses known as G and V series agents. G series agents include; Sarin, Soman, Tabun. This is also classified because the initials of the short names of these titles begin with G. V series are also available. In 1864, the first organophosphate compound, tetraethyl pyrophosphate, was produced. This synthesis was carried out by Wurtz (13). Many times, these agents have been used in various incidents or wars. E.g; Germany produced about 12 thousand tons of this material during WWII (2). AChE, interplay with the "catalytic triad" characterized by 3 amino acids: ser, glu and his (14). The remaining positive part of the chain interacts with the anionic region known as the choline binding moiety. The oximes used for therapeutic purposes can break the covalent bonds and re-activate the enzyme. However, the presence of this enzyme in the environment causes the phosphonium residues to turn into a second substance. This substance can also cause aging. Sensitivity to these organophosphate compounds varies from person to person. Because everyone's genetic is different and genetic susceptibility is important in this regard. These substances can also directly interact with cardiac, muscarinic and glutamate NMDA receptors. When the half-time is examined; 2 minutes for soman whereas 40 hours for tabun (15). When the adverse effects of AChE inhibitors are observed; pupillary contraction, bronchial narrowing, increased movement of the stomach and intestinal tract, and increased sweating may be occur. These agents which cause skeletal contractions can also cause paralysis. When the effect on the brain is examined; loss of consciousness and ataxia can be seen. It can even cause coma. Even death can occur after bronchial obstruction (16). The lethal dose of Sarin (GB) is known as half a milligram for human tissue. This ratio is less visible, but the lethality of cyanide is 500 fold less than GB (2). It appears that GB is extremely dangerous.

Choking agents

Choking agents are chemical substances which cause pulmonary edema, reduced pulmonary compliance and altered gas exchange as a result of pulmonary inflammation when they are inhaled. Choking agents which are used as chemical warfare agents are phosgene (carbonyl dichloride, $COCl_2$), diphosgene, chlorine and chloropicrin. They are irritant, corrosive and/or chemically highly reactive gases or aerosols. Water-soluble choking agents tend to damage the upper airways and alveoli while water-insoluble choking agents tend to damage the lower airways.

Phosgene (carbonyl dichloride, $COCl_2$) is a colorless gas at room temperatures and it is a liquid at low temperatures and heavier than air. It smells like musty hay. Its boiling point is 8,2°C and melting point is -118 °C. It is insoluble in water however, soluble in benzene, toluene and acetic acid. It decomposes to HCl and carbon dioxide when it reacts with water as shown below;



$$COCl_2 + H_2O \rightarrow 2HCl + CO_2$$

Davy synthesized the phosgene in 1812. It was utilized by Germany and during WWI and it caused to 1069 casualties and 120 deaths. Unfortunately it has been utilized to product drug, stain, pesticide and polyurethane since WWII. Phosgene binds to TRP receptors (TRPA1 and TRPV1) in sensory nerve terminals (C fibers) in the airways. This binding leads to neurogenic inflammation especially in the lower airways and alveoli with the postreceptor mechanisms mentioned in the mustard gases. As a result of neurogenic inflammation bronchial constriction, extravasation, alveolar damage, apoptosis and pulmoner edema may occur. Therefore, insufficient gas exchange emerges. Its binding to glutathione and amino-thiol groups of biomolecules leads to deterioration of antioxidant mechanisms (depletion of glutathione and increase in ROS formation), alveolar cell damage, apoptosis, deterioration of alveolar architecture and therefore pulmoner edema. It decomposes to HCl and carbon dioxide when it reacts with water in the airway. Also, HCl contributes to alveolar damage and apoptosis. Following exposure, first, a latent period (2-48 hours) is observed, after then coughing, burning in the throat and eyes, choking and dyspnea occurs (2,6). Although primary target of phosgene is lung, it leads to skin irrritation and erythema when it is inhaled (2).

Diphosgene is a colorless, water-insoluble fluid at room temperature. Diphosgene hydrolyzes to HCl in moist air conditions. It was used by Germany during WWI. Diphosgene was described after first use of phosgene because it was believed that diphosgene could destroy filters of gas masks. There is a use of diphosgene in some

laboratory preparations. Its mechanism of action and clinical features of its exposure are similar to phosgene (6).

CarlWilhelm Scheele discovered the chlorine in 1774. It was utilized as a chemical warfare agent in WWI by Germany in 1915 in the Second Battle of Ypres. It was also utilized during the Iraq War in Anbar Province in 2007. Chlorine ($_{17}$Cl) is a poisonous gas at room temperature and soluble in water. It has a pale yellow-green color and it smells like mixture of pepper and pineapple. Its density is 3,2 g/L, melting point is 175,6 °C and boiling point is 239,11°C. Since it is heavier than air, it tends to accumulate on the floor. There are many using area of chlorine in industry. For instance, it is utilized in water disinfection, severage and refuse treatment, pesticide, rubber and solvent production, as bleach (2). Chlorine's target organs are moist surfaces such as eyes, skin, upper and lower airways. Since chlorine gas has intermediate water solubility, it affects the upper and the lower airways (17). Less than 10% inhaled chlorine gas can reach the hypopharynx when low concentrations are inhaled (18). It can reach the lower airways when high concentrations are inhaled (17). Chlorine is a strong oxidizing agent and it reacts with water in moist surfaces such as eyes, skin, upper and lower airways. When it reacts with water, hypochlorous and HCl occur. Therefore, hypochlorous acid (HOCl) decomposes into HCl and an oxygen free radical as shown below;

$$H_2O + Cl_2 \longleftrightarrow HCl + HOCl \longleftrightarrow 2HCl + O^-$$

HCl reacts with S–S bonds, hydroxyl groups and amide groups on cell surface proteins. HOCl reacts with S–S bonds sulfhydryl groups and amide groups (17,19,20). These interactions associated with cellular glucose uptake, loss of cellular K+, cell swelling, inhibition of glycolysis and ultimately cell lysis (21). HCl and an oxygen free radical cause tissue damage and inflammatory processes in the lung. Thus, alveolar-capillary membrane is disrupted. As a result of these alterations, fluid accumulation in the lung, hypoxia and hypoxemia occur. Chlorine gas inhalation causes burning in the upper airways, eyes, chough, wheezing, nausea, chest pain, dermatological manifestations such as erythema and vesicles. Within 2-4 hours, it can lead to acute lung injury and dyspnea (2,22-24). In physical examination, wheezing, rales, decreased breath sounds, tachypnea and increased work of breathing can be observed. If pulmonary edema has not occurred, chest radiography is commonly negative on presentation. Generally, initial arterial blood gas is normal. Obstructive, restrictive or combined pattern dysfunction can be shown by pulmonary function tests (25,26).

Chloropicrin (tri-chloro(nitro)methane) is an oil which has colorless and a faintly yellow fluid, also it is not as toxical as phosgene but more toxical than chlorine. It decomposes to phosgene and nitrosyl chloride at 112 °C. Vaporized form is highly toxic. Chloropicrin was used in WWI. Its use in warfare is obsolete after WWII. It is used to sterilize soil and seed, to kill fungi and insects, for production of fumigants. Chloropicrin has toxicity mechanism same with chlorine (2). Chloropicrin poisoning has three periods including irritation, latent (2-5 h) and lung edema (27). It is believed that it leads to low grade rabdomyolizis when it is inhaled (28). Also, it penetrates filters of gas masks and causes vomiting (2).

Asphyxiants/blood agents

Asphyxiants/blood agents including hydrogen cyanide (HCN), cyanogen chloride (ClCN) and arsine are agents which cause tissue hypoxia. They lead to hemolysis or deterioration of oxidative phosphorylation (6). ClCN is a colorless gas at normal temperature. It has a pepper-like odor. Its boiling point is 13,8 °C. It is used for production of herbicides, ore refining and to clean metals. It was used during WWI by the French. Since it could penetrate the masks, U.S. produced around 11,000 tons ClCN (2). ClCN contacts with water in the airways and decomposes to ammonia, hypochlorous acid, HCl when it is inhaled. Ammonia, HOCl and HCl irritate the airways and induce choking (6). HCN binds to methemoglobin, the non-oxygen-transporting Fe (III) form of hemoglobin and it does not disrupt oxygen transport in the blood. Cyanide anion of HCN inhibits cytochrome c oxidase in mitochondria, thus, leads to deterioration of oxidative phosphorylation and cellular ATP deficiency (2,6). ClCN causes dyspnea, headache, dizziness, concern, palpitations, mydriasis, blurred seeing, nausea and numbness when it is inhaled in low concentration. It causes hyperventilation, unconsciousness, convulsions, fixed dilated pupils when it is inhaled in high concentration. Exposure to high concentrations leads to death from respiratory and/or cardiac arrest within minutes. Cyanides should be suspected when persistent hypotension, metabolic acidosis, normal arterial oxygenation, and extreme venous oxygenation are present and nerve agents are excluded. Also, cyanides can cause mass fatalities (2).

HCN is a uncolored flammable fluid with boiling point 25,6 °C. It is used in pharmaceutical industry, for production of plastics, as fumigant. It was first produced by Schele in 1782 and was used by France in WWI (2). HCN binds to methemoglobin, the non-oxygen-transporting Fe (III) form of hemoglobin and it does not disrupt oxygen transport in the blood. Cyanide anion of HCN inhibits cytochrome c oxidase in mitochondria, thus, leads to deterioration of oxidative phosphorylation and cellular ATP deficiency. It causes signs and symptoms which are similar to ClCN exposure's. Lethal concentrations of HCN are 270 ppm, 181 ppm and 135 ppm for 6-8 min, 10 min, 30 min, *respectively* (2,6).

Arsine is a colorless highly inflammable gas which has a slight garlic smell and water-soluble and soluble in many organic solvents. It is used for production of organic chemicals and lead storage batteries. Arsine has not been used as a chemical warfare agent because of its low toxicity. Nonetheless, arsine, the most toxic form of arsenic, is a potential chemical warfare agent (2,6). It is believed that arsine causes massive hemolysis of red blood cells by formation of hydrogen peroxide and adducts with oxyhemoglobin and interaction with the sodium-potassium pump, red blood cell swelling and bursting

(29,30). Lastly, massive hemolysis generally leads to renal failure (31,32).

Behavioural agents/incapacitating agents

Incapacitating agents are described as agents used to neutralize enemies in the United Kingdom, August 1963 (33). These agents can also cause various cognitive problems, especially temporary injuries. After WWII, the United States began to investigate the effects of these substances on human body. These substances include lysergic acid diethylamide (LSD-25), ketamine, etc. It has been used to suppress terrorists in several countries including Moscow. The two most dangerous features of behavioural agents are being odorless gas and hanging in the air for 3-4 weeks. It is an important feature that it can easily remain on most surfaces such as opaque, water. As a result of the use of these agents, all of systems and organs are affected. Central nervous system and respiratory system are mainly affected targets. Influences of these agents on the nervous system are endless restlessness, cognitive process impairment and tremor. These effects can result in coma or even death. There are many effects such as bulging, vomiting and changes in heart rate, number of respirations and body secretion (2).

Protection, Decontamination and Treatment

Exposure to chemical agents is a damaging event, therefore protective measures must be taken, exposed people must be removed from the area, decontaminated and treated to minimize the damage. Rescuers must be use personal protective equipment during decontamination and removal of exposed persons. In the treatment, primarily, ABC (Airway, Breath and Circulation) approach and supportive treatment should be applied. In case of need, specific antidote may be administered, unfortunately only a few agents have specific antidote (34). Clinical features and pharmacological treatment of chemical agent poisoning are summarized in the Table 2.

Sulfur mustard has no specific antidote and supportive treatment must be applied. Primarily, exposed people must be removed from the area by rescuers. All clothes should be removed and packed in plastic bags, person should be bathed. For erythematous skin lesions, the use of topical cortisone may be useful. Larger bullae's roof must be removed with saline irrigation and antibiotics (silver sulfadiazine or modified Dakins solution) must be applied to peeled fields. Also, irrigation, topical antibiotic and steroids are necessary to protect the eyes. Bronchospasm requires bronchodilators and glucocorticoids. Granulocyte colony-stimulating factor, blood transfusion or even bone marrow transplantation may be necessary for the treatment of bone marrow suppression (2).

Nitrogen mustard has no specific antidote and treatment is similar to sulfur mustard (2).

In the lewisite exposure, supportive treatment is applied, exposed people must be removed from the area by rescuers. All clothes should be removed and person should be bathed. Lewisite has specific antidote as called British Anti-Lewisite (dimercaprol, BAL) (2). BAL was discovered in Great Britain during WWII for the treatment of lewisite exposure. BAL is dispended in 10% solution in peanut oil and administered by intramuscular injection as 100 mg/ml. BAL forms chelation complexes which are relatively nontoxic substances with arsenicals and other heavy metals(lead, mercury) by its sulfhydryl groups and increases the rate of excretion of arsenicals and other heavy metals. Chelation complexes are excreted in both urine and bile. Other chelating agents including 2,3-dimercaptopropane 1-sulfonate (DMPS), meso 2,3 dimercaptosuccinic acid (DMSA) and the mono and dialkylesters of DMSA can be use (35,36).

Table 2. Clinical features and pharmacological treatment of chemical agent poisoning

Chemical Warfare Agent	Signs and Symptoms	Pharmacological Treatment
Mustard agents	Blisters, erythema and edema on the skin, itching, photophobia, eye pain, cough, pain sensation in the airways, dyspnea, nosebleed, nausea and vomiting, seizures	Supportive treatment; For skin: Topical cortisone, Silver sulfadiazine or Modified Dakins solution For Eyes: Topical antibiotic and steroids For Bronchospasm: Bronchodilators and Glucocorticoids
Lewisite	Blisters, burning sensation and painful erythema on the skin etc. (similar with mustard agents), hypovolemia and refractory hypotension	Spesific antidote: Dimercaprol (BAL) Alternatives: DMPS, DMSA etc. Supportive treatment
Nerve agents	Myosis, dyspnea, gastrointestinal hipermotility, sweating, skeletal contractions and paralysis, unconsciousness, ataxia	Atropine, oximes, diazepam, midazolam, pyridostigmine bromide Ketamine and HU-211*
Phosgene Diphosgene	Choking, dyspnea, coughing, burning in the throat and eyes	Supportive treatment N-acetylcysteine and ibuprofen**
Chlorine Chloropicrin	Dyspnea, burning in the upper airways and eyes, chough, nausea, chest pain	Supportive treatment
Hydrogen cyanide Cyanogen chloride Arsine	Choking, dyspnea, hyperventilation, eye irritation, mydriasis, headache, palpitations, nausea, convulsion, fixed dilated pupils	For Hydrogen cyanide and Cyanogen chloride specific antidotes: nitrites, dicobalt edentate hydroxycobalamine/ thiosulfate For arsine Supportive treatment
Behavioural agents	Cognitive problems, tremor, bulging, vomiting and changes in heart and respiratory rate	Supportive treatment

*Ketamine and HU-211 were tested for neuroprotection and clinical trials revealed good results (2)

**N-acetylcysteine and ibuprofen can be useful in phosgene induced lung injury (2)

The management of nerve agent exposure includes decontamination, respiratory support and specific antidotes. All clothes should be removed and skin should be decontaminated by plenty of water or sodium hypochlorite solution because steams can be trapped in clothes. There is a skin decontamination kit approved by The Food and Drug Administration (FDA) including activated charcoal impregnated with ion exchange resins (Ambergard) (2). Atropine can be used for the treatment of nerve agent exposure. It is an anticholinergic drug which blocks muscarinic AChE receptors on effector cells at parasympathetic (and sympathetic cholinergic) neuroeffector junctions in the peripheral ganglia and central nervous system. Thus, all effects of AChE and its congeners at muscarinic receptors can be competitively inhibited by atropine (37). MARK I kits, which contain 2 mg atropine in an auto injector form for use intramuscularly are given to U.S. military personnel. 2, 4 or 6 mg atropine can be administered as loading dose in field. Treatment can be repeated every 5-10 min until the patient's secretions are dry. Oximes also can be used for treatment of nerve agent exposure. Oximes act by reactivating cholinesterase. Oximes reverse cholinergic effects of AChE on muscarinic and nicotinic receptors. MARK I kits mentioned above also contain auto injectors of 600 mg of 2-pralidoxime chloride (2-PAM Cl). 2-PAM Cl's initial field loading doses are 600, 1200 or 1800 mg. It is suggested that 1000 mg 2-PAM Cl is administered via slow intravenous drip over 20-30 min with no more than 2000 mg over a period of 1-1,5 h (2).

There are limited options for the treatment of seizures induced by nerve agents: diazepam, midazolam etc. The fastest acting and most effective benzodiazepine is midazolam, but diazepam is equally effective in field. Diazepam is given to forces as 10 mg injectors for intramuscular use (2).

Pyridostigmine bromide can be used in a dose of 30 mg every eight hourly before exposure to rapidly acting agents such as soman for wartime use. It should not be used after the exposure. Pyridostigmine binds reversibly with cholinesterase; thus more deadly soman can not bind with cholinesterase. Bioscavangers including plasma-derived butyrylcholinesterase and recombinant butyrylcholinesterase were developed. These bind and detoxify nerve agent entering circulation (38). Ketamine and HU-211 were tested for neuroprotection and clinical trials revealed good results (2).

In the ClCN exposure, rescuers have to wear protective and impermeable clothes with breathing apparatus. Casualties must be evacuated by rescuers. Dilute detergent solution should be used for skin decontamination using a "rinse-wipe-rinse" technique. There are three specific antidotes including nitrites, dicobalt edentate and hydroxycobalamine/thiosulfate. Ten milliliters of 3% sodium nitrite can be administered intravenously over 5-20 min. If intravenous access is not achieved, one 0,2 ml ampoule amyl nitrite can be applied through inhalation over 0,5-1 min followed by sodium thiosulfate (25 ml of a 50% solution intravenous over 10 min) (39). Nitrites transform hemoglobin to methemoglobin. Affinity of methemoglobin to cyanide is stronger than cytochrome oxidase. So that, toxicity is prevented. Sodium thiosulfate separates sodium cyanide and methemoglobin from each other by forming sodium thiocyanate which is removed from the body and methemoglobin is converted back to hemoglobin. Dicobalt edetate can be administered intravenously over 2-5 min in doses of 300-600 mg, but it has severe cardiovascular side effects. Hydroxycobalamine/thiosulfate has minimal adverse effects so that it is the drug of choice in case of ClCN exposure. Treatment of HCN exposure is similar to ClCN (2).

In the arsine exposure, well-protected rescuers should evacuate the casualties. Unfortunately, there is no specific antidote, yet. High flow oxygen should be given to patients. When there is severe hemolysis, exchange transfusion should be applied. To prevent renal failure, forced alkaline diuresis can be applied. Hemodialysis should be begun to patients with renal failure. In the chlorine exposure, well-protected rescuers should remove the casualties from the area. Unfortunately, there is no specific antidote, yet. All clothes should be removed and applied supportive medical care. The treatment of chloropicrin exposure is similar to chlorine (2).

In the phosgene exposure, well-protected rescuers should remove the casualties from the area. Unfortunately, there is no specific antidote, yet. All clothes should be removed. Casualties should be bathed with soapy water for decontamination. Symptomatic and supportive treatment are required. Patients should be watched up to 48 hours. For the patients surviving more than 48 h, the prognosis is very good (40). In experimental studies, it was shown that N-acetylcysteine and ibuprofen can be useful in phosgene induced lung injury (2).

There is no spesific antidote to reverse the effects of 3-quinuclidinyl benzilate definitively. It is stated that physostigmine treatment is not very effective for 3-quinuclidinyl benzilate exposure. Supportive treatment is required. For the markedly agitated patients, benzodiazepines is an option (2).

As a conclusion, chemical warfare agents which have been used for a long time are still source of hazard for people and environment despite all the prohibitions. These agents are incapatitating, damaging, toxic and lethal compounds and they cause severe morbidity even mortality. Prohibitions must be increased and made deterrent. Except prohibitions, especially rescuers and all people should be informed about these agents (protection, decontamination, treatment) (2). Knowledge about pharmacological properties of the antidots and other drugs, used in the treatment of exposure to chemical agents will be important in order to reduce severity of injury and to increase survival in patients.

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