



Mustards

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Introduction

Blistering agents, also known as vesicants, were introduced as weapons during World War I. These agents were not generally lethal but greatly incapacitated enemy troops who had little or no protection from them. At that time, sulfur mustard was the agent seen on the battlefield. Two decades later, chemists learned that the sulfur group could be replaced by nitrogen and a new class of vesicants was developed.

Overview: the Mustards

Sulfur mustard, with the military designation of HD, was first synthesized in 1822. Its chemical name is 2,2' di(chloro-ethyl) sulfide and it gained its name mustard gas on the battlefields of World War I because of its distinct garlicky, mustard odor. In 1935, on the eve of World War II, a new class of mustards called the nitrogen mustards was developed. There are three variations of nitrogen mustard with the military designations HN1, HN2, and HN3. Their respective chemical names are shown on the slide.

Of these agents, sulfur mustard and the HN3 variation of nitrogen mustard are the most feared and of greatest concern. Sulfur mustard poses the greatest terrorist threat because it is inexpensive to manufacture and can be dispersed in droplet or vapor form. These agents are highly stable and their persistent in the environment. In addition, they can attack not just the skin, but the eyes, mucous membranes, lungs, and blood-forming organs as well. And for those unfortunate enough to become victims of the mustards, there is no specific treatment. Exposure to mustard is often weeks to months of sometimes-painful recuperation.

Overview: Toxicity

The mustards are highly toxic and, as stated, can attack a variety of organs in the body. The most likely routes of contamination are skin exposure and inhalation.

In terms of relative risk, the skin offers the greatest protection and requires an exposure of 200 mg-min/m³ to inflict serious burns. Such burns can result from either liquid or vapor contact. The lungs will be damaged with an exposure to the vapor at 100 mg-min/m³. However, the eyes are the most sensitive and an exposure to just 10 mg-min/m³ of the vapor or liquid can produce serious corneal damage.

Protection

The mustards are the most difficult chemical agents to protect oneself against. They can penetrate a wide variety of natural cell membranes such as wood, leather, rubber, and various plant fibers, as well as most man-made materials. Ordinary clothing and even the highest quality surgical protective gear offer no protection against the mustards. It is possible to protect the skin with a paste containing chloramine, but this is effective only against very low level exposures and, of course, cannot protect the eyes, membranes, or lungs. The best option is full military-grade protective gear with a respirator, NBC suit, gloves, and overboots. However, the mustards can slowly penetrate even these materials and this equipment must be changed and discarded on a regular basis.

Detection

Under certain conditions, the mustards form colored complexes with para-nitrobenzpyridine. This makes it possible to detect even minute amounts of liquid agent using readily available single and three-color detector papers. For wide area detection, monitoring devices for local contamination and testing kits are commercially available, and regional or state emergency management and military contacts can provide you with these sources.

From a clinical perspective, the mustards are among a handful of chemicals for which laboratory testing is available to detect chemical presence in the body. Mass spectrometric and immunoassay methods applied to blood samples, as well as urinary thiodiglycol levels, can now be used to confirm exposure.

Decontamination

The importance of decontamination following an attack with mustard agents cannot be sufficiently stressed enough. Decontamination must be efficient and quick since a drop of these agents on the skin can cause serious damage within 2 minutes. It is also important to know whether the agent involved is sulfur or a nitrogen mustard since chemical inactivation using chlorination is effective against sulfur mustard (HD), but considerably less so against HN3. There are also special considerations if thickened mustards are used. These are mustard agents that have been combined with non-volatile solvents such as chlorinated rubber, to form a gelatinous substance that is difficult to remove from the skin. Such thickened agents must first be scraped off with a knife or similar hard object. The

exposed surface must then be wetted with a cloth drenched in an organic solvent, such as unleaded gasoline, to break down the base solvent. Then the usual decontaminating procedures can proceed.

Dermal exposure is likely in any mustard attack on unprotected victims. The decontamination of skin involves either physical adsorption of the agent using an adsorbing powder such as Fullers earth or talcum powder, or a combined approach using chemical inactivation plus adsorption. The latter is effective against sulfur mustard and involves adding a chlorinating compound, such as chloramine, into the adsorbing powder. The chlorinating compound may also be added to ointments, solutions, or organic solvents and used to inactivate the mustard agent. One word of caution here, water should not be used to decontaminate skin exposed to mustard agent as this can spread the agent and worsen the exposure.

Decontamination

The eyes and mucous membranes are too sensitive for the compounds used to decontaminate the skin, and these compounds will irritate the conjunctivae and mucous membranes. For exposure to these areas, copious irrigation with water, isotonic sodium bicarbonate, or normal saline is required with the goal of diluting and removing the agent from these tissues. If possible, irrigating solution, should be contained so as to avoid further contact with it.

Wounds may also become contaminated with mustard agent and special care must be taken to decontaminate such injuries. The most common form of contamination is through materials such as cloth, bullet, or missile fragments that might be carried into the wound. These wounds must be explored fully using a no-touch technique and any foreign materials must be removed and placed in a chlorine solution to prevent off-gassing of the mustard vapor. Once debrided, the wound should be well irrigated using a dilute "Milton" solution of 3000 to 5000 parts per million of free chlorine. This solution must be allowed to dwell in the wound for roughly 2 minutes before being flushed clear with normal saline.

A word of warning: this applies to soft-tissue and extremity wounds. Do not use these irrigation methods in the thoracic or abdominal cavities, or with intracranial head injuries.

Signs and Symptoms

The earliest signs and symptoms of mustard agent exposure depend on the route of contact. Ultimately systemic effects will occur, as will be discussed in a subsequent slide.

As stated earlier, the eyes are the organs most sensitive to mustard, requiring a fraction of the exposure levels of skin or the lungs before serious damage occurs.

Ophthalmic injury can be divided into four classifications. The least serious is a mild conjunctivitis that will resolve spontaneously in 1 to 2 weeks. A higher level of exposure can produce a severe conjunctivitis with minimal corneal involvement. This includes blepharospasm, edema of the lids and conjunctivae, and orange-peel roughening of the cornea and typically requires 2 to 5 weeks for healing. The third classification is mild corneal involvement with erosions that stain green with fluorescein and where revascularization, superficial corneal scarring, iritis and temporary relapses are possible complications. This level of injury requires hospitalization and can take up to 3 months to heal. The most serious ophthalmic injury involves severe corneal involvement with ischemic necrosis of the conjunctivae. Temporary blindness may occur, but permanent blindness is very rare. Convalescence may take several months and late relapses are possible.

Signs and Symptoms

The hallmark of dermal contact to the mustards is a symptom and sign-free period that occurs for several hours post-exposure. The duration of this latent phase, as well as the severity of subsequent lesions, is dependent upon several factors such as gas versus liquid exposure and the individual sensitivity of the victim. In addition, environmental conditions have a role, with high temperatures and humidity producing a shorter latent phase and more serious injuries.

There is a sequence of reaction to a dermal mustard exposure. Following a latent phase of 2 to 48 hours, a striking erythema will develop accompanied by intense itching and slight edema. As the erythema fades, the area will become hyperpigmented. With a more serious injury the involved area will progress to develop thin-roofed, fragile blisters that typically are not painful but can feel tense and uncomfortable. These blisters break easily, leading to suppurating and necrotic wounds. The most serious dermal injury by mustard agents is a serious chemical burn that can result in full thickness skin loss. The areas most prone to such loss are the genital and axillary regions, although any part of the skin may be burned. These damaged tissues are covered with slough, extremely susceptible to infection, and slow to regenerate, leading to a long, sometimes painful, period of recuperation.

Signs and Symptoms

Following mustard exposure a latent period also occurs in the respiratory tract. This phase, usually lasting 4 to 6 hours, is followed by irritation and congestion of the nasal cavity and pharynx, as well as irritation of the epithelial lining of the trachea and larger airways. This irritation starts with rhinorrhea, a burning pain in the throat and hoarseness. Damage to the vocal cords can result in complete aphonia. A dry, painful cough will develop and progress into one that is highly productive of copious airway secretions and necrotic epithelium. Fragments of this necrotic material can also result in airway obstruction with coarse rales and

dyspnea becoming evident on exam. Infection becomes a major complication within 48 hours. In the most serious exposures, the victim typically dies from pulmonary edema and mechanical asphyxia due to obstruction, or from rampant bacterial infection facilitated by an impaired immune response.

Signs and Symptoms

One additional route of exposure not commonly seen is via the gastrointestinal tract. This occurs when contaminated food or water is ingested, and contact with the mustard agent produces destruction of the mucous membranes of the GI tract. Such damage will produce nausea, vomiting, abdominal pain, diarrhea and prostration from severe fluid losses. The emesis and stool are often bloody and with significant blood and fluid losses, hemorrhagic shock can occur.

Once completely absorbed, the mustard agents produce a variety of systemic effects. One of the most serious effects of sulfur mustard and HN3 is the resultant damage to the blood-forming organs, primarily the bone marrow. These agents can deplete the marrow of all of its elements. Granulocytes and megacaryocytes appear more susceptible to damage than cells of the erythropoietic system and within the first few days a reactive leukocytosis occurs, quickly followed by a profound leukopenia. With involvement of the erythropoietic system, aplastic anemia is also a possible complication. The occurrence of a severe leukopenia and aplastic anemia portends a grave prognosis.

Other systemic signs include those similar to radiation poisoning: headache, nausea, and vomiting, as well as the previously mentioned leukopenia and anemia. Gastrointestinal pain is common, even in the absence of GI tract exposure. At high doses, central nervous system effects can also be seen with CNS excitation and convulsions, followed by a serious CNS depression. In addition, cardiac abnormalities can occur, consisting of irregular rhythms, various atrio-ventricular blocks, and even cardiac arrest.

Treatment

As mentioned earlier, there is no specific antidote or treatment for mustard toxicity. The aim of therapy is to prevent infection, relieve symptoms, and promote healing. Fortunately, the great majority, 97%, of mustard agent casualties survives.

There are a few caveats to remember in the treatment of mustard injuries. First, when treating the eye, do not use topical anesthetics for pain relief, as they may increase corneal damage. Use systemic, narcotic analgesics when needed. Similarly, do not bandage the eyes; use protective goggles. In cases of dermal exposure, relieve the intense pruritis with cool compresses or corticosteroids in solution. Do not use creams or ointments, which may increase the risk of infection. And finally, with inhalation injuries, treat pulmonary symptoms

symptomatically and be especially alert for pneumonia. The organisms most likely to produce problems are those typically found in nosocomial infections: enteric gram negative rods, streptococcus pneumoniae, Hemophilus influenzae, and methicillin sensitive staphylococcus aureus, as well as anaerobes, Legionella, Acinetobacter, and pseudomonas aeruginosa. Methicillin resistant staph (MRSA) must also be considered if encountered in your hospital. Empiric treatment would follow the ATS 3 guidelines for severe pneumonia with risk factors. This includes ciprofloxacin or an aminoglycoside, plus either piperacillin, piperacillin/tazobactam, a third generation cephalosporin, aztreonam, or imipenem. Vancomycin should be considered if MRSA is suspect.

Long Term Medical Sequelae

Victims of mustard exposure are likely to experience significant long-term complications, including emotional issues similar to post-traumatic stress syndrome. These include prolonged psychological manifestations of chronic depression, loss of libido, and anxiety. In addition, there are local effects dependent upon the route of exposure that may include visual impairment, scarring of the skin, chronic bronchitis, bronchial stenosis, and an increased sensitivity to the agent. The eyes in particular may take months to heal and, although rare, eye damage may result in a delayed keratitis 6-10 years post-exposure with late-onset blindness. Over an even longer term, sulfur mustard is a known carcinogen causing an increased incidence of lung and laryngeal cancer.

Environmental Sequelae

Because of their physical properties and stability, the mustards are known for being highly persistent in the environment, posing a risk for additional exposures weeks or even months after an initial attack if the area has not been thoroughly decontaminated. This is even truer in cold and temperate climates, and with agents that have been thickened by dissolving them in a non-volatile solvent. Such agents are difficult to remove with common decontamination methods.

Summary

In summary, the mustards can be devastating agents on the battlefield or in the hands of terrorists. From a military perspective, sulfur mustard and the nitrogen mustard designated HN3 are of greatest concern. Sulfur mustard is the mustard most likely used by terrorists as it is the cheapest and easiest of these agents to manufacture. The mustards possess certain properties that make them particularly hazardous. They are chemically stable and persistent in the environment. They readily penetrate most materials, even military-grade NBC gear. They attack the eyes, mucous membranes, skin, lungs, and blood-forming organs leading to serious local and systemic effects including death by pulmonary edema and

mechanical asphyxiation secondary to airway obstruction, as well as by fulminant infections helped by immune system compromise.

Immediate decontamination is critical since serious injury can occur within 2 minutes of exposure and the initial signs and symptoms are dependent upon the route of exposure and typically include a latent phase. With no specific antidote or treatment, the goal of therapy is to relieve symptoms, prevent infection and promote healing, with an emphasis on preventing infection. The good news is that the great majority of victims, 97%, survive.