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OBSERVATION AND CLINICAL MANIFESTATIONS OF PATIENTS INJURED WITH MUSTARD GAS

H. SOHRABPOUR, M.D

From the Department of Medicine, shahid labbafi-Nejad Medical Center, Shahid Beheshti university of Medical Sciences, Tehran, Islamic republic of Iran.

ABSTRACT

More than five hundred chemically injured patients were admitted to the Labbafi-Nejad Medical Center in Spring of 1984. These patients were of two groups. The majority of patients had extensive skin burns, eye injuries as well as respiratory problems, and a second group of patients suffered mainly from neuromuscular and psychological problems.

In this report, clinical manifestation and observations of the first group, as well as a summary of the therapeutic modalities adopted are presented. We conclude that chemical weapons have a devastaring effect both in short and long term on humans and a more influential stance should be taken by responsible organizations to stop their use.

INTRODUCTION

In 1915, the first reports regarding chemical attacks were published. Chlorine was the first substance utilized and caused many casualties. As respirators became avialable, all efforts were directed toward finding more toxic agents, which led to the discovery of phosgene and hydrogen cyanide. Other efforts aimed at the production of substances such as chloropicrin, which is hardly absorbed by masks. The most important trend however was toward the production of mustard gas and arsenical vesicants which cause skin damage and render respirators ineffective. Between 1920 to 1930, many other agents were discovered but none of them gained popularity more than phosgene and mustard gas. During the second world war, the first series of nerve gases known as G-agents were introduced, which included soman, sarin and tabun. In 1955, a new class of nerve gases known as V-agents were discovered. These agents are quite stable and thus are very difficult to neutralize.[1]

Tables I and II compare the respiratory as well as percutaneous lethal doses of some chemical agents.

The number of substances that have been classified as chemical warfare agents exceeds one hundred compounds. Candidates for chemical warfare should have certain physicochemical, biological and toxicological

TABLE I. COMPARISON OF THE RESPIRATORY LETHAL DOSE OF SOME CHEMICAL AGENTS.

PHOSGENE	50 Mg
SARINE	1 Mg
V-AGENTS	0.1 Mg

TABLE II. COMPARISON OF THE PERCUTANEOUS LETHAL DOSE OF SOME CHEMICAL AGENTS.

MUSTARD GAS	5000 Mg
SARINE	1000-2000 Mg
V-X	5 Mg

properties. In addition, the cost of production should also be contemplated. Considering all these factors, nearly sixty substances have been chosen as chemical warfare agents, and are classified as follows:

A) Lethal agents: Used to either kill or injure the enemy severely enough to necessitate evacuation or hospitalization.

B) Incapacitating agents: Used to put the enemy completely out of action for several days or hours, but recovery may be possible without medical aid.

C) Harrasing agents: Used to disable the enemy for as long as he remains exposed.

In Table III, a more ditailed classification is shown.

PATIENTS, MATERIAL AND METHODS

From the beginning of the imposed war, there have been sporadic chemical attacks against the Islamic forces in different parts of the battle fronts, but after the beginning of the "Kheibar" operation in March, 1984, extensive chemical attacks were launched against Iranian troops, causing many casulities,[2] 528 of whom were admitted to the Labbafi-Nejad Hospital. The age distribution of these patients is shown in figure1.

The majority of these patients had symptoms and signs of mustard gas poisoning,[3] which will be described, and a few complained of nonspecific neuromuscular symptoms.

According to the patients, the main source of chemical agents have been aerial bombs and artillery shells. Figure 2 shows one of the bombs found in the battle zone.

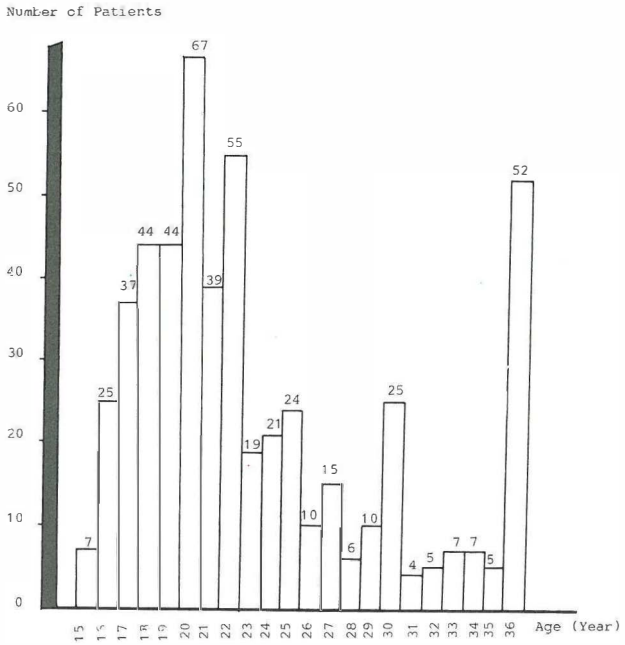


Figure 1. Age distribution of the patients admitted to the Shahid Labbafi-Nejad Hospital.

Figure 2. A chemical bomb dropped in 1984.

RESULTS

Symptoms and Signs:

I- *Ophthalmologic manifestations.* Almost all of the patients noticed a foul smelling odor and some decribed it as a "garlic smell" and after an interval of 1-3 hours, eye irritation, a burning sensation and lacrimation ensued. These symptoms were followed by blurred vision, photophobia and severe pain in the eyes, such that the patients felt blind. On examination, lid edema was prominent. Blepharokeratoconjunctivitis of different degrees and corneal abrasion were also seen. Only two patients had corneal ulcers and three cases suffered from iritis and nasolacrimal duct obstruction due to severe lid burns. Figure 3 shows a patient with acute conjunctivitis due to mustard gas poisoning.

II- *Skin Lesions:* After an interval of 8-24 hours, the first dermatological symptoms appeared, which consisted of pruritus and a burning sensation. These symptoms were more severe in moist areas of the body such as the groin, armpits, and base of the neck. Initially erythema was seen and after two to three days, blisters appeared. These blisters were initially about 0.5×0.5 cm, but could grow rapidly to cover large areas of the skin. They contained a yellowish and gelatinous material (figure 4).

Skin burns covered between 15 to 60% of the body surface. In the groin and on the scrotum, the burns were quite painful and followed a more protracted course. Penile edema was also present in these cases. All parts of the skin except the palms, soles and scalp were affected. Areas of pigmentation and discoloration of the skin lasted for lengthy periods of time in some of the patients.

III-*Respiratory problems:* Two distinct syndromes could be noticed:

a) Upper airway involvement. This began 24-48 hours after exposure and was manifested by a sensation of choking, cough, burning of the throat, dysphonia

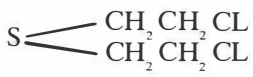
TABLE III. CLASSIFICATION OF CHEMICAL AGENTS.

A. LETHAL AGENTS

1. *LUNG IRRITANTS:* $COCL_2$, PHOSGENE, CARBONYL CHLORIDE

2. *BLOOD GASES:* I. hydrogen cyanide (HCN)
II. cyanogen chloride (CLCN)

3. *VESICANTS* (BLISTER AGENTS), MUSTARD GAS (YPERITE):



4. *NERVE GASES (ORGANOPHOSPHOROUS COMPOUNDS)* (I)-G AGENTS:

I, GA tabun
II, GB sarin
III, GD soman

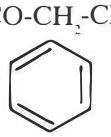
5. *OTHER LETHAL CHEMICAL AGENTS* (II)-V AGENTS:

I, VE
II, VM
III, VX

6. OTHER LETHAL CHEMICAL AGENTS
(I) - aryl carbamate
(II) - naturally occuring toxin proteins:
I, ricin
II, botulinal toxin

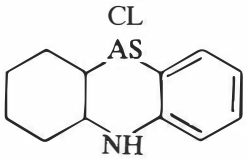
B. 1. BACTERIAL ENTEROTOXINS AND RELATED SUBSTANCES (STAPHYLOCOCCAL ENTEROTOXIN)
2. PSYCHOCHEMICALS I-L.S.D: (N, n-diethyl lizergamide)
II-AGENT BZ

C. HARASSING AGENTS (SENSORY IRRITANTS): I, -CN (W-chloroacetaphenone)



II. CS (O-CHLOROBENZYLMALONONITRILE)

III-DM (adamsite) CL AS NH



D. ANTI-PLANT AGENTS:
agent orange
agent white
agent blue (cacodulic acid)
bromacil
monuron

and dysphagia. Physical examination including laryngoscopy revealed signs of acute pharyngitis and laryngitis. Edema and hypermia of the mucosa was prominent. In the pure form of this syndrome, patients did not have dyspnea or hemoptysis.

b) Lower airway involvement. This group of patients were more critical, they all had shortness of breath and cough which was more severe and continuous. Cough was productive and sputum was mucoid. Physical examination revealed tachypnea, on occasion more than 30/minute, as well as tachycardia. Blood pressures were stable except in cases of respiratory arrest. Auscultation of the chest revealed generalized wheezing and rhonchi as well as fine crepitations in the lung bases. A group of these patients developed adult respiratory distress syndrome (ARDS), manifested with severe hypoxemia (PO_2>45mm Hg) and increased alveolar-arteriolar gradient irresponsive to high concentrations of 0_2. In this particular group of patients, prognosis was poor and mortality was quite high. It should be mentioned that many patients were febrile in the first few days, which could have been due to the intoxication itself.[3]

One case ARDS who was intubated and had developed collapse of the left lower lobe underwent bronchoscopy and the author noticed severe inflammation and sloughing of the mucosa which had virtually occluded the lower lobe bronchus, and pieces of nec-

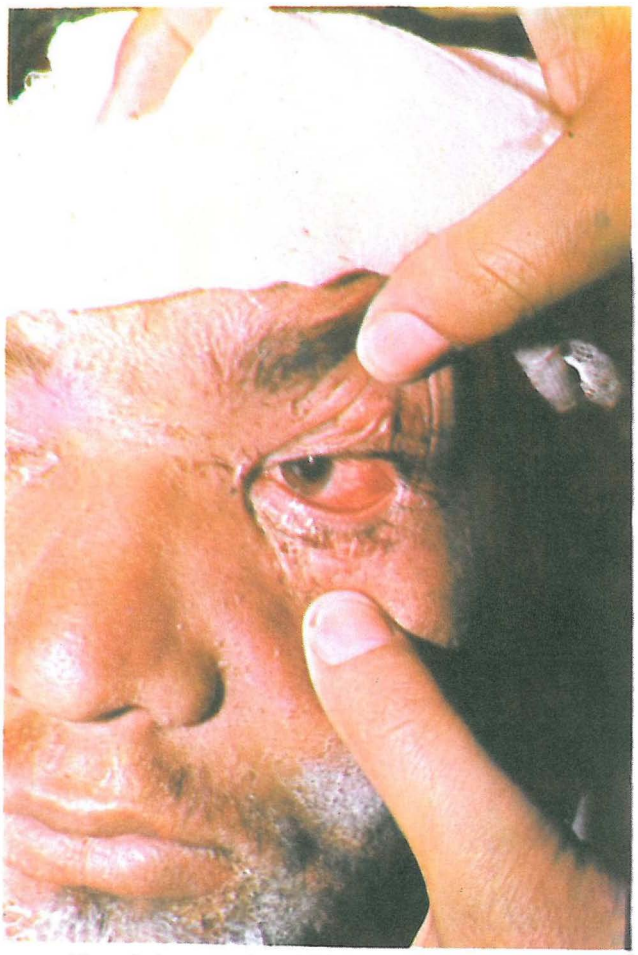


Figure 3. Acute conjunctivitis due to mustard gas.

trotic tissue had to be removed by forceps.

Pulmonary function studies were performed on 64 cases, the results of which are presented in Table IV.

IV-*GI symptoms* were much less frequent, although most of the patients had nausea and vomiting in the first few hours. Hematemesis was noticed in only one case, who had a history of duodenal ulcer. Liver function tests were also normal, except for a moderate elevation of LDH, which returned to normal after a few days.

V-*Hematological complications.* These are usually a relatively late manifestation of mustard gas poisoning in comparison to other complications. Leukocytosis was the first manifestation which occurred initially. WBC counts of up to 25000/mm^3 were seen. This was followed by leukopenia in some patients between 10 to 14 days later. WBC counts occasionally dropped to less than 1000/mm^3. Most of the leukopenic patients had extensive skin burns. Bone marrow studies revealed hypocellularity affecting all elements, with normal iron stores. Mild anemia was noticed in some cases, and coagulation profiles were normal.

VI-*Infection.* This complication was common and is in fact a major cause of death.[4] The skin and respiratory systems are especially prone to infection. Streptococci species and *Pseudomonas aerogenosa* were isolatod from the wounds and sputum of some of the patients. In cases of bacterial pneumonia, patients usually ran high fevers and radiographs disclosed segmental or patchy infiltrates.

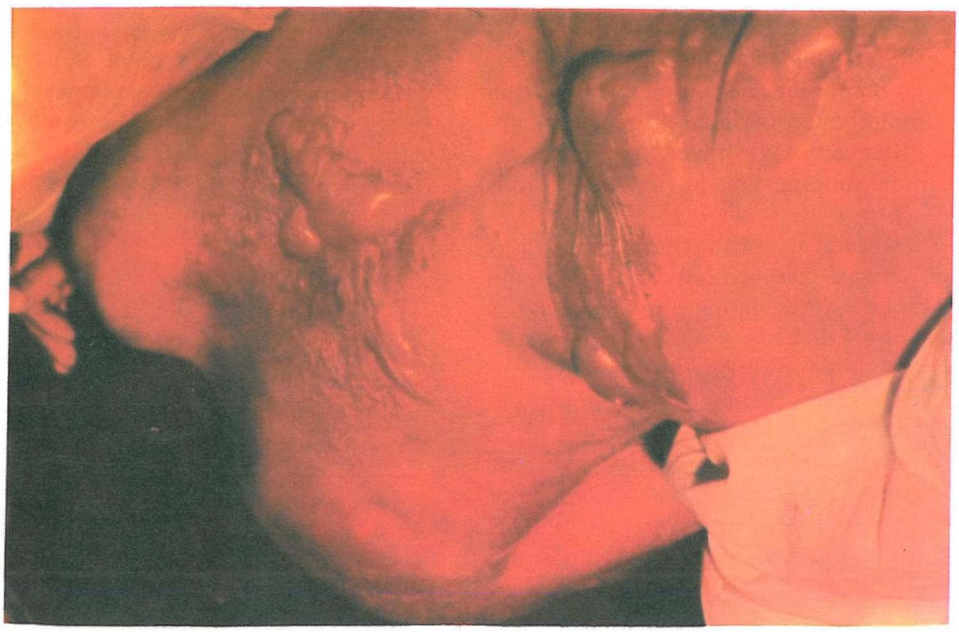


Figure 4. A. Typical blister formation in exposure to mustard gas.

TABLE IV. RESULTS OF SPIROMETRIC STUDIES.

Total no of patients	64	100%
Obstructive pattern	34	53.13%
Restrictive pattern	1	1.56%
Obstructive. & restrictive pattern	12	18.75%
Normal pattern	14	21.88%
Unacceptable	3	4.84%

Treatment

It must initially be emphasized that protective masks and overgarments are very important to prevent serious damage to the tissues. There are certain immediate steps to be followed at the site of exposure.[5] An outline of a symptomatic treatment protocol accepted by our institution is given below.

For opthalmologic symptoms: Irrigation with Ringer's solution, application of 1% cyclopentolate solution four times daily, application of 20% sulfacetamide solution four times daily. Corticosteroid compounds should not be used until complete healing of corneal epithelium. Prognosis is good and pratically all of the patients recover fully.

For skin burns: I.V. fluids according to the clinical status of the patients, daily bathing with tapwater, application of silver sulfadiazine ointment to the skin lesions. Skin should be left exposed unless burns are of high degree. Recovery takes place in about 2 to 3 weeks, but pigmentation persists for lengthy periods of time.

Treatment of respiratory problems is more difficult. In upper airway involvement, use of heated nebulizers is helpful. Antihistamines and mucolytics are used, but their efficacy is questionable. In severe cases of laryngitis, systemic corticosteroids are administered intravenously for the first 48 to 72 hours and then switched to oral prednisone (30-40 mg) for 2 weeks, with tapering and discontinuation over the course of one month. Patients who had tachypnea of more than 30/min or hypoxemia (PO_2 ‹60 mmHg) were closely observed and were intubated and mechanically ventilated if the criteria of ARDS were met.[6]

Positive end expiratory pressure (PEEP), had to be applied in all of these cases, and prognosis was poor. In cases of leukopenia (WBC‹3000/mm³) patients were kept on reversed isolation, and if WBS counts dropped to less than 200/mm³ a combination of cephalosporins (8 mg/daily) or carbenicillin (20 gm/daily) along with gentamycin (3-5 mg/kg/day) were utilized. If WBC counts dropped below 1000/mm³, leukocyte transfusion was initiated according to the guidelines of the Blood Transfusion Organization of Iran.[7] Overall mortality of our patients calculated to 4.8% (fig. 5).*

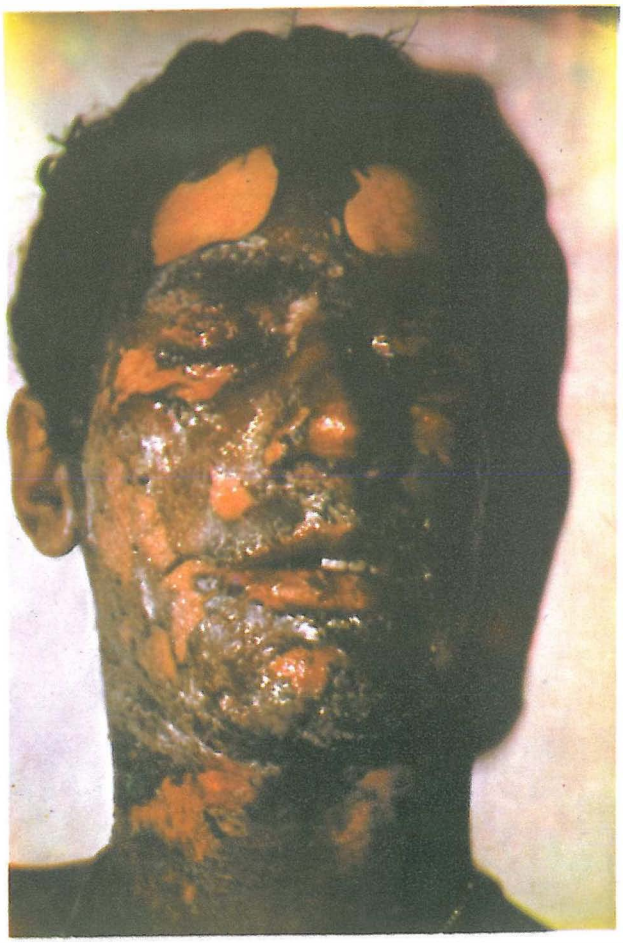


figure 4. B. Severe skin burns due to mustard gas exposure.

DISCUSSION

Mustard, synthesized in 1922 is a 2, 2 di(chloroetlyl) sulfide, S(CH2-CH2-Cl). By substituting the sulfur atom with a nitrogen atom, nitrogen mustard is produced which has the same vesicant properties.

* This figure pertains to the most severely injured patients who were admitted to our department. The majority of the injured patients however were treated as outpatients, and had a much lower mortality rate. The patients assessed in this study reflect the first major group of chemically wounded Iranian forces. In subsequent Iraqi chemical affacks, more effective anti-chemical warfare measures were utilized, resulting in a significant decline in morbidity and mortality.

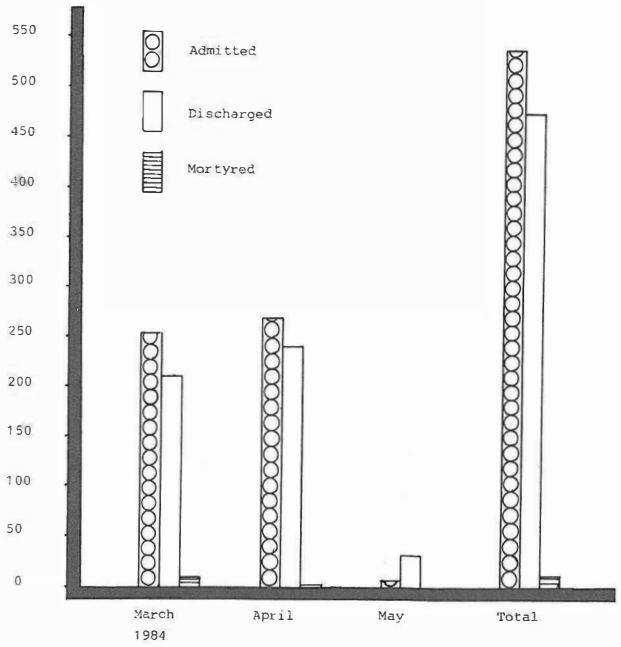


Figure 5. Total number of admitted, discharged and martyed persons due to chemical bombing in March, 1984.

Due to its alkylating and electrophilic properties, mustard can modify the structure of nucleic acids, cellular membranes and proteins by combining with certain functional groups for which it has a great affinity. Therefore, mustards can react with amine groups, carboxy groups, S-H groups, OH and primary phosphate groups. From the biochemical point of view, mustards have three distinct effects: cytostaticity, mutagenicity and cytotoxicity. The available data clearly indicate that DNA is the most sensitive target in cells. In this respect, the action of mustards resembles that produced by ionizing radiation, and mustards have been called "radiomimetic" compounds. The most important reaction of mustards with DNA is the cross linking of the two complementary strands, and the monofunctional alkylation of the nitrogenous bases. The former interferes with DNA synthesis and the cellular division process. The high cytotoxicity of polyfunctional mustards towards the more actively proliferating cells in the body can be attributed to this reaction. The latter reaction (alkylation of DNA bases, predominantly guanine and adenine) is much less lethal to the cell, but because they alter genetic information, they result in point mutation.

Since DNA is responsible for the synthesis of messenger RNA and ultimately proteins, alterations in DNA can interfere with the formation of structurally and functionally competent proteins and enzymes.

Mustard compounds have a devastating effect on the human body. Although blisters caused by mustard gas may heal in 2 to 3 weeks, they are often followed by a corp of furuncles generelly on and around the burned area. There is a general lowering of resistance after mustard gas poisoning; therefore an increased susceptibility to infection such as influenza, bronchitis, pneumonia and tuberculosis results.[1] Chronic bronchitis and emphysema develop in many patients who have been exposed acutely. The mutagenic effects of mustard compounds have been proven by Szirma and Salzgeler in chickens and rats.[1]

The carcinogenic effects of mustard in rats were demonstrated by Heston in 1953.[1] In workers of the mustard industry, the incidence of lung cancer has increased ten-fold.[8]

The incidence of chronic bronchitis and subsequent death attributed to cancer of the lung and pleura among British war prisoners who suffered from mustard gas poisoning have been quite high.[1] Follow ups of our own patients show a high morbidity rate, especially chronic obstructive lung disease, among those exposed to mustard gas.

Unfortunately, the Iraqi government has used these anti-human weapons repeatedly despite all international treaties,[9] and even after being condemned by the United Nations Security Council.[10] It is evident that we all shall have to witness more tragic events unless serious action is taken to stop them.

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