Long-Term Complications of Sulphur Mustard Poisoning in Intoxicated Iranian Veterans

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ABSTRACT

Introduction: Sulphur mustard (SM) is an alkylating chemical warfare agent that was widely used during the Iran-Iraq conflict (1980–1988). Delayed complications of SM in different organs were evaluated in this study.

Methods: This cross-sectional study was performed from March 2005 to June 2006. The Veterans Foundation provided us with the files of all chemical warfare–poisoned patients in the province of Fars, Iran. Clinical manifestations, laboratory data, and demographic characteristics of the patients were recorded from their files and a face-to-face interviews. Data analysis was performed by student *t* test statistical method.

Results: A total of 134 patients were enrolled in the study. The age range of the patients was 32–45 (37.2 ± 9) years. SM poisoning was confirmed 19.5 ± 1.6 (17–22) years after initial exposure. The duration of exposure in patients was 13.35 ± 8.7 (1.5–48) hours. The most common complication was found in the lungs (100%), skin (82.84%), and eyes (77.61%). The most frequent medications used for the treatment of these complications were: bronchodilators, drugs used for dermatological problems, and drugs used for ocular complications. Analytical study showed no association between the age of exposed patients and the severity of toxic complications ($p > .05$), but there was a significant association between the duration of exposure and the number of complications ($p < .05$).

Conclusion: Results of this study indicate that respiratory complications generally increase over time. Therefore, follow-up of veterans exposed to SM is recommended. This may lead to early diagnosis of SM complications and help prevent the late manifestations of this toxicity.

INTRODUCTION

Sulphur mustard (SM) was first synthesized in 1822 by Desprets, then in 1860 by Nieman and Gutherie. It was one of the major chemical warfare agents developed and used during World War I. Its last military use was in the Iran-Iraq war. SM injured >100,000 Iranians, one-third of whom are still suffering from late effects [1]. Complications of SM exposure in humans include ocular and dermal injury, respiratory tract damage, reproductive and developmental toxicity, gastrointestinal effects, hematological effects, and cancer [2]. SM is absorbed by inhalation, through the skin, or through the gastrointestinal tract. After absorption, it undergoes intramolecular cyclization to form an ethylene episulfonium ion intermediate, which in turn reacts with and alkylates nucleic acid and proteins, resulting in impaired cell homeostasis and eventually cell death [3].

Although several studies have been performed in Iran regarding SM poisoning [3,4], there has only been 1 study performed in the southern region of Iran [5]. This study showed the diversity of the effects of SM gas inhalation on the respiratory system

Keywords: sulphur mustard, poisoning, Iranian veterans

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10 years after initial single exposure. The aim of this study was to evaluate the prevalence of the late complications of SM 20 years after the initial exposure in a veterans' clinic in the south of Iran.

MATERIALS AND METHODS

The Veteran Foundation (chemically-injured veterans' clinic of Fars province) provided us with the files of all chemical warfare agent–poisoned patients in the province of Fars, Iran (3400 files). The information was gathered randomly from March 2005 to June 2006. The files were reviewed and patients who met the following criteria were selected:

1) Documented exposure to SM
2) Clinical complication due to SM poisoning in at least 1 target organ (e.g., lung, skin, or eyes)

Clinical manifestations, paraclinical data (electrocardiography, echocardiography, pulmonary function test, bronchoscopy, high-resolution computed tomography, and endoscopy), lab data (cell blood count, urinalysis, urine culture, and liver function test), and demographic characteristics of the patients and their drug histories were recorded from their files. Clinical and laboratory data were only used to confirm diagnosis. Time of exposure to SM and complications were documented after a face-to-face interview with the patients. Patients with proven systemic illnesses before exposure to SM; with a history of cigarette smoking; those exposed to asbestos, coal dust, silicone, or cotton dust; and patients who worked in petroleum industries were excluded from the study. The number of organ systems involved and drug classes for each complication used were counted for each patient and the mean ±SD were reported.

Statistical Analysis

The data were analyzed utilizing a student *t* test methodology run on the SPSS version 11.5 software (SPSS Inc., Chicago, IL, USA). A p value of <0.05 was considered to be significant.

RESULTS

A total of 134 patients fulfilled the criteria and were enrolled into the study. The age range of the patients was 32–45 (37.2 ± 9) years. The mean ±SD years after initial exposure were 19.5 ± 1.6 (17–22). The mean duration of exposure was approximately 13.35 ±8 .7 (1.5–48) hours. Most complications were found in the lungs (100%), skin (82.84%), and eyes (77.61%). Other organs involved included the central nervous system (CNS, 58.21%), cardiovascular system (43.28%), and the genitourinary (40.30%) and gastrointestinal tracts (35.07%).

Complications and drug classes used for their treatment are described in detail below. Some patients received more than one drug class for the treatment of each complication.

Respiratory Complications:

All patients complained of dyspnea, 72.38% suffered from coughing, and 52.98% from expectoration.

Based on the clinical and paraclinical findings, common respiratory complications were diagnosed as chronic bronchitis in 49 (36.57%), asthma in 30 (22.39%), bronchiectasis in 21 (15.67%), chronic obstructive pulmonary disease in 16 (11.94%), small airway disease in 15 (13.64%), and restrictive airway disease in 3 (2.72%) patients. The most common drugs that were used for the treatment of respiratory complications were corticosteroids (administered orally or via inhalation or injection, 68.66%) and antibiotics (administered orally or parenterally, 31.34%).

Dermal Complications

The most common signs and symptoms were itching (78.36%), dry skin (60.44%), burning sensation (60.44%), blisters (24.62%), scarring (17.91%), dermatitis (13.34%), and pigmentary changes (hypo- or hyperpigmentation, 11.19%).

These complications were located on the back (46.5%), genitalia (37.5%), the front of the chest and abdomen (35%), lower extremities (33%), upper extremities (mainly axillary, 30%), and the head and neck (13%).

Moisturizing agents (49.25%), oral antihistamines (26.12%), and sunscreen agents (22.39%) were the most frequent drugs used in the treatment of skin complications.

Ocular Complications

The signs and symptoms were recorded as burning sensation (68.65%), photophobia and red eye (63.64%), itching and foreign body sensation (63.43%), dry eye (61.19%), blepharitis (27.61%), corneal ulcer (11.94%), tearing (11.9%), and retinal and conjunctiva complications (4.48%).

The most common drugs administered for the treatment of ocular complications were cycloplegics (43.28%), ophthalmic antibiotics (32.38%), ophthalmic corticosteroids (25.37%), and artificial tears (17.16%).

Neurological Complications

The most common neurological complications were headache (26.86%), epilepsy (16.42%), vertigo (11.94%), and tremor (4.48%). Antiepileptic drugs (19.4%) were the most common neurological drugs used in these patients.

Cardiovascular Complications

Chest pain (25.37%) and palpitation (17.91%) were the most frequent symptoms, and hypertension was the most common complication that was recorded.

Coronary artery bypass graft was performed in 8 cases.

The most common drugs used for the management of these conditions were antianginals (15.67%) and antihypertensives (14.18%).

Urogenital Complications

The highest incidence of urogenital disorders was sexual dysfunction (32.58%), including anorgasmia and impotence. Other urogenital disorders reported included urinary tract infections (11.19%), pain and burning sensation in the urinary tract (6.71%), and incontinence (3.73%). Sildenafil (in 25 patients) and antibiotics (in 13 patients) were the most common drugs used for treating urogenital complications.

Gastrointestinal Tract Complications

Pain and a burning sensation in the stomach (23.13%) and gastrointestinal tract bleeding (1.5%) had the most and least frequency in this category, respectively. Other complications included acid hypersecretion (15.67%), chronic constipation or diarrhea (6.7%), anorexia (3.73%), and peptic ulcer (4.48%). Acid secretion inhibitors (proton pump inhibitors, H2-blockers) were used mostly for treating the gastrointestinal complications.

Some psychiatric problems were also reported in our patients, including anxiety (25.37%), irritability and nervousness (23.13%), major depression (21.64%), and post-traumatic stress disorder (11.94%), respectively.

The mean ± SD number of organ systems involved and drug classes used in our patients were 3.4 ± 1.6 and 2.3 ± 0.8, respectively.

Analytical Analysis

Exposure times of ≤24 hours were associated with 11.54 ± 4.17 toxic signs and symptoms in 33 patients, whereas exposure times of >24 hours were associated with 15.54 ± 4.63 toxic signs and symptoms in 101 patients ($p < .0001$). There was not any significant association between the age of the patient at the time of exposure and frequency of any of the organ system involved ($p > .05$).

DISCUSSION

Mustard is very lipophilic and therefore can penetrate epithelial tissues easily. The eye, respiratory tract, and skin of unprotected persons most likely will be damaged after exposure to SM. It causes acute, chronic, and delayed toxicity [1].

The first report on the delayed toxic effects of SM poisoning in 236 Iranian veterans revealed that the most common effects were on the respiratory tract (78%), CNS (45%), skin (41%), and eyes (36%). These effects were reported 2 and 28 months after exposure [6].

In a study performed by Khateri et al. on 34,000 Iranians, the most common complications observed 13–20 years after exposure to SM were in the lungs (42.5%), eyes (39.3%), and skin (24.5%) [4].

In a study by Balali et al., the toxic effects of SM exposure in a group of 40 severely intoxicated Iranian veterans 16–20 years after initial exposure were described. The most commonly affected organs in this study were lungs (95%), skin (75%), and eyes (65%) [3].

The results of our study were comparable to previous studies; lung, skin, and eyes were the most common organs showing the late toxic effects of SM exposure. The frequency of these toxic effects, however, differed from previous studies. There are some causative factors for this difference, such as sample size, time of detoxification, time passed from initial exposure, air pollution, and environmental conditions.

Inhalation of SM mainly affects the upper respiratory tract, leading to airway disease. To date 45,000 Iranians are suffering from late respiratory complications due to mustard gas exposure [7]. In fact, airway disease has been reported as the most common complication of SM in most studies [3,4,7,8]. The most commonly affected organ in the current study was the lung, in which an obstructive pattern of disease predominated over a restrictive pattern; this compares favorably to previously reported studies. However, respiratory-tract complications occurred more frequently. The result of this study and others showed that the frequency of bronchiectasis tends to increase over time. One reason for this is the increase in the incidence of respiratory infections due to immunodeficiency in patients [9,10]. The present study demonstrated a significant association between the duration of SM exposure and number of organ systems involved. Ghanei et al. reported that patients with moderate to severe exposure to SM had a higher risk of pulmonary complications compared to persons with mild SM exposure [11]. In this study, we did not determine the correlation between level of SM exposure and risk of specific organ complications. In a study performed by Emad et al., a positive correlation was shown between patients' age at time of exposure and the severity of pulmonary complications [5]. However, in our study age at time of exposure did not have a significant impact on frequency of any of the organ systems involved. Most of our patients were in the age range of 14–25 years at the time of exposure. Therefore the odds for late complications in our population were high and duration of treatment was long.

Skin disorders are one of the major complications in SM exposure. The most common skin complaints among patients were itching followed by burning sensation and desquamation. These symptoms are due to dryness of the skin, thus become worse in dry weather and after physical activity [8,12]. Comparison with other studies showed an increase in the frequency of itching and dry skin. This may be due to the warm and dry climate of Shiraz. Pruritus is the most common complication reported in most studies [3,4,12]. Panahi et al. reported that 53% of SM-intoxicated patients had severe pruritus, resulting in a significant negative impact on quality of life [13]. The most important lesion was reported to be malignant change [12].

High temperature and the level of skin moisture are the most important factors increasing the severity of skin damage. Skin at moist body areas (axilla, scrotum, and anal region) has a lower dermal barrier function and therefore is more sensitive. In our patients, the location of dermal complications was quite consistent with these anatomical regions.

The eyes have the most sensitivity to SM. This marked hypersensitivity is attributed to several ocular features, including

the aqueous-mucous surface of the cornea and conjunctiva, as well as higher turnover rate and intense metabolic activity of corneal epithelial cells [14]. Nearly 90% of eye injuries due to SM exposure later show some kind of ocular symptoms (e.g., ulcerative keratitis) [15]. In this study burning sensation, photophobia, red eye, and itching were the most common complications comparable to other studies.

Complicated skin reactions such as psoriasis, discoid lupus erythematous and vitiligo—as well as hematological and complicated ocular reactions with SM—have been reported in previous studies [8,10,14]. These complications were not recorded in this study, as these patients were directly referred to subspecialized clinics.

The only late neurological complications of SM that were studied and reported were neuropathy and neuromuscular lesions [3,16,17]. Thomsen et al. suggested that persistent damage to the nervous system is probably a frequent complication in persons exposed to mustard gas that results in chronic neuropathic symptoms [16].

SM is a so-called "radiomimetic drug." It may damage the gastrointestinal tract, bone marrow, and central nervous system [18]. Although animal studies were performed to evaluate SM toxicity on various organs such as the kidney and the reproductive system [19,20] and there has been a report of malignant gastrointestinal tract transformation [21] after SM exposure, there are no reports concerning long-term nonmalignant complications of the gastrointestinal tract, cardiovascular, central nervous system, and genitourinary tract. In our study, these complications were recorded; however, we cannot imply that these complications were truly due to SM toxicity because we did not include an aged-matched control group and there are no previously published reports of these complications in Iranian veterans. So far, only one study has evaluated the late cardiovascular complications of SM. In this study, Gholamrazanezhad et al. observed that patients intoxicated with SM are more susceptible to coronary artery disease or mild cardiomyopathic changes in comparison with normal controls [22]. Only one case report of late cardiovascular complication of SM exposure cannot be a definite cause of late complication of SM poisoning, and more studies are necessary.

It appears that psychiatric problems are more related to the trauma caused by the war itself rather than SM poisoning. Moreover, there has been no reporting of such problems.

One limitation of our study was the fact that the complications reported may have been due to other drugs or conditions (psychiatric problems). Another limit to this study was the probability of a recall bias. Although patients' files were used for most data collection, data collected from interviewers may have caused a recall bias in our study. In fact, we had to exclude an important factor (time to onset of complications) from our data collection because of this problem. The third limit to this study was that there were no records of complicated skin (malignant transformation) and other malignant complications, since these patients were directly referred to subspecialized clinics.

We conclude that the most common late complications of SM poisoning affect the respiratory tract, skin, and eyes. These patients have received many drugs for the treatment or management of multiple organ diseases. Therefore, they are at high risk for complications of drug interactions and adverse drug reactions.

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