

REVIEW PAPER

Treatment for Sulphur Mustard Poisoning – A Review

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ABSTRACT

Sulphur mustard (SM) is a chemical warfare agent of historical and current interest. It is a well known blistering agent or vesicant. SM was extensively used in world war I as a chemical weapon and has been stockpiled by several countries since that time. SM serves as an ideal war gas and is favoured militarily for its ability to incapacitate rather than to kill. Its use resulted in large numbers of casualties requiring prolonged and intensive medical care. Despite Geneva Protocol of 1925, which categorically banned the production, stockpiling and use of chemical weapons in wars, SM has been used in several wars, including the Iran-Iraq war during the 1980s, which renewed interest in it. Though, the chemical weapons convention was signed by more than 160 countries in 1993 and was subsequently ratified by several countries, the threat from this agent persists due to its clandestine usage during war and also by terrorist groups. There is no effective and specific antidote for local and systemic toxicity of SM despite scientific research for more than 75 years. Many compounds were tested as antidotes for SM, but very few of them have been shown to provide some protection. The present review is aimed at evaluating the treatment regime and other clinical measures used to treat SM victims and the various drugs and chemicals screened as antidotes for SM poisoning in experimental animals.

1. INTRODUCTION

Sulphur mustard (SM) or mustard gas [1,1'-thio bis (2-chloroethane)] is a powerful blistering agent that produces extensive injuries at the site of exposure. It is one of the oldest known alkylating agents and due to its potent incapacitating action, it is called as 'king of war gases'. The first military use of SM as a chemical weapon was made during world war I (1917) by Germans against British troops at Ypres in Belgium. This resulted in many casualties due to lack of protective clothing and ineffective medical treatment^{1,2}. The physico-chemical properties of SM are given in Table 1.

After world war I, Britishers showed concern about carrying out their own strategic research on

chemical warfare (CW) agents. For the first time, basic biochemical research on CW agents and SM was initiated independently by Dixon³ and Peters⁴ at Cambridge University and Oxford University, respectively. Later, the first clinical description of the blisters and the lesions caused by SM was documented by Peters as 'biochemical lesion'⁵.

SM is a frequently used CW agent^{6,7}. Despite the signing of chemical weapons convention in 1993 and its subsequent ratification by several countries, the possibility of SM being used clandestinely during a war or by terrorists still exists due to the simple method of its preparation. Hence, research is being carried out on the identification of better decontamination agents and

Table 1. Physico-chemical properties of sulphur mustard

Properties of SM	Values/details
CAS registry No.	[505-60-2]
Chemical formula	$C_4H_8Cl_2S$
Molecular weight	158.08
Vapour density	5.8
Liquid density at 25 °C	1.27
Boiling point	217 °C
Freezing point	14.46 °C
Vapour pressure (mm)	0.069 at 20 °C
Decomposition temperature	149 - 177 °C
Hydrolysis at 25 °C	
(a) Rate	8.5 min
(b) Major products	Thiodiglycol and chloride
Solubility in	
(a) Water at 25 °C	0.8 g/l
(b) Organic solvents	Readily soluble

antidotes for SM. Hundreds of chemicals and drugs have been evaluated for their antidotal efficacy against SM. But their efficacy is not satisfactory. The present review is aimed at giving a description of the decontamination agents and antidotes for SM evaluated to date. To understand the use of various antidotes, a brief description of the mechanism and effects of SM is also given.

2. MECHANISM OF SULPHUR MUSTARD TOXICITY

SM is a bifunctional and highly reactive agent. It is documented as a genotoxic, mutagenic and carcinogenic agent. At high dose levels, it exerts cytotoxic effects^{8,9}. Chemistry and biological fate of SM have been investigated and reviewed extensively^{9,10}. SM owes its toxicity to spontaneous formation of highly reactive and unstable sulphonium compounds. These compounds undergo intramolecular cyclisation and can react with a wide variety of molecules of biological interest, including proteins and nucleic acids. DNA is one of the major targets of SM, producing inter-strand and intra-strand adducts, leading to DNA strand breakage.

Several hypotheses have been proposed about SM-induced toxicity. According to Papirmeister,⁹ SM-induced DNA breakage leads to activation of chromosomal enzyme poly (ADP-ribose) polymerase, which in turn, depletes cellular NAD⁺, inhibits glycolysis, and ultimately causes cell death¹¹. Another mechanism proposed for SM-induced cytotoxicity is based on lipid peroxidation occurring due to the formation of reactive oxygen intermediates as a consequence of glutathione (GSH) depletion^{9,12}. Still another mechanism is based on the hypothesis that depletion of GSH can increase intracellular Ca^{2+} causing cell death⁹. Since SM is a highly reactive molecule, it can interact with a wide variety of biomolecules leading to a condition similar to apoptosis or necrosis. Increased excretion of uric acid in urine, usually observed in such conditions, is also observed following SM administration in experimental animals, either topically or through inhalation.

3. TARGET ORGANS

Eyes, skin and respiratory tract are the principal target organs of SM toxicity. SM in liquid, vapour or aerosol form attacks all the target organs and causes injuries.

3.1.

Eye is the most vulnerable organ. Its exposure to SM at 0.001 g m³ concentration for 1 hr can cause irritation, itching, lacrimation, burning sensation, conjunctivitis and photophobia¹³. Moderate and severe effects are marked hyperemia, perforation in the anterior chamber and corneal lesions. Studies on rabbit eyes indicate that SM-induced injury to the cornea is characterised by degeneration of epithelial cells, and the lesions are similar to those in human victims. Keratopathy was also observed in some war veterans¹³. Large scale exposure to SM results in a number of severe eye lesions like corneal opacities, corneal ulceration, delayed recurrent keratitis, chronic conjunctivitis and keratoplasty⁹.

3.2 Skin

SM penetrates the skin without appearance of any warning signal, such as itching or burning. SM is a highly lipophilic compound and gets absorbed very quickly. However, the symptoms may appear after a latent period of 6-24 hr, depending upon the severity of exposure. Certain regions of the body are particularly susceptible to skin damage, because of their higher temperature and humidity. The vulnerable regions are pubic area (particularly the scrotum), the under-arms, the neck, the skin between the fingers and between the toes, and the area around the eyes^{9,14}. After one day, blister formation on the epidermis reaches its peak and it may be painful. Serous fluid containing leukocytes accumulates in the blisters. SM generally causes severe injury in fur covered animals, because of a thin epidermis and densely packed hair follicles¹⁵. The skin of these animals does not vesicate. However, the lesions are similar to those observed in humans. The necrotic epidermal tissue sloughs off after one week, and the granulating process starts at the border. Histologically, heavy exudations of serum and erythrocytes are detected. The blisters result in harmful ulcers, which heal very slowly and tend to become infected. If they do not heal (after a month), deep marginal pigmentation often develops.

3.3 Respiratory Tract

Inhaled SM injures the respiratory epithelium from the nasopharynx to the bronchioles. Incapacitating airway injury occurs through vapour exposures that are significantly lower than those producing severe skin blisters. In case of recent war-exposed humans, symptoms like cough, chest pressure, sinus pain, sore throat and hoarseness have been observed on immediate exposure¹⁴. However, the symptoms progress into bronchospasm, bronchiolar obstruction by sloughed epithelium and secretions, haemorrhagic pulmonary edema, and secondary pneumonia over a period of time. Death after SM exposure generally occurs due to bronchopneumonia and secondary infections. Severe exposure can also lead to

respiratory failure and death. Mice exposed to SM vapours showed sensory irritation during exposure and airway obstruction later¹⁶. Cancer of respiratory tract, nasopharynx, larynx and lungs have been reported in SM-exposed victims¹⁰

4. CLINICAL MANAGEMENT OF SM VICTIMS

Information on clinical treatment of persons exposed to SM has been reported since world war I, from cases of exposure during wars, laboratory or industrial work, experimentation on animals, or sometimes, deliberate voluntary exposures. However, substantial addition to knowledge has come after the Iran-Iraq conflict, and now improved clinical management of SM victims has become possible as highly sensitive and selective laboratory parameters are available¹⁷.

4.1 Treatment for Eye Effects

Exposure of the eyes to SM, even at low dose can be incapacitating. Although, eye is one of the target organs, only limited studies on animals have been reported. The pathological findings are similar to those for most chemical injuries. On exposure to liquid SM or its vapours, the eyes should be washed with uncontaminated water as quickly as possible. Since SM gets absorbed rapidly, washing should be done within 2 min.

Momeni¹⁸ treated SM victims from Iran by irrigating with Ringer's solution and applying 1 per cent cyclophenolate or 15 per cent sulphacetamide in hydroxy propylmethyl cellulose or chlorotetracycline eye ointment. Borak and Sidel¹⁹ suggested that patients with SM ocular injuries should be treated in the same way as for other chemical injuries. Severe corneal ulceration may require months to heal. The general treatments for eye lesions are listed in Table 2.

4.2 Treatment for Skin Effects

SM may persist as a liquid on contaminated skin, clothing, leather and equipment for many hours or days depending on physical conditions. Battlefield protection against SM exposure requires wearing of gas mask, protective clothing and gloves (physical protection). Special materials are used

Table 2. Treatment for eye effects

Symptoms	Treatment
Contamination of the eye	Wash with uncontaminated water within 2 min
Sticky eyelids	Sterile petroleum jelly
Severe photophobia	Pilocarpine or neostigmine
Secondary infection	Two drops of sodium sulphacetamide should be instilled (30 %) every 4-8 hr. Chlorotetracycline eye ointment chloramphenicol, gentamicin and neomycin can also be used.

for making protective clothing, since cotton, rubber and latex are no barriers for the entry of SM. Generally, butyl rubber is used for providing physical protection. To improve the ability for physical protection, a number of materials with very good adsorptive capacity, like activated carbon, can be impregnated in the clothing.

SM penetrates the skin rapidly and should be decontaminated immediately. A variety of physical and chemical methods are available for this purpose (Table 3). If the decontamination is not carried out immediately, the skin will be affected by liquid SM. In the absence of a satisfactory antidote for SM, decontamination is given the priority. Medical personnel attending on SM victims should also wear protective clothing and prior precautions should be taken to decontaminate the skin.

Momeni¹⁸ studied the cases of 535 Iran war victims and suggested the following treatment for skin manifestations of SM: Daily bath with dilute (1/10,000) $KMnO_4$ solution, and local application of calamine, promethasine containing lotion, caladryl lotion or sterile petroleum jelly. Skin ointments like 1 per cent silver sulphadiazine, 0.2 per cent nitrofuracine and 1 per cent hydrocortisone were also recommended.

Blisters were aspirated, big bullae were opened and open wounds were kept on sterile sheets. Patients who experienced severe pain during dressing were given morphine sulphate. A variety of antibiotics were used both locally and systemically. Urinary catheter was used for those

Table 3. Decontamination agents for SM

Agents	References
Physical agents	
Fuller's earth	20,21
Charcoal	22
Talcum powder	23
Tissue paper	23
Flour	23
Abrasives	23
Salad oil	23
Household detergents	23
Chemical agents	
DS-2	24
FOPS	24
Povidone iodine	22
Trichloroacetic acid	25
Thiodiglycolic acid	25
Bleaching powder or Calcium hypochlorite	2,9
Potassium permanganate	2,9
0.5 % HTH	23
Chloramine-T	2
Dichloramine-T	2
CC-2	20,21
M-5	26

patients with severe genital skin damage. Various treatments recommended for SM skin lesions are listed in Table 4.

4.3 Treatment for Respiratory Effects

For SM victims with severe respiratory problems, endotracheal intubation should be considered. If airway obstruction precludes intubation, cricothyroidectomy may be performed. Inhalation of moist air and use of mucolytics, such as *N*-acetyl cysteine, are prescribed for patients with respiratory complaints. Supplemental oxygen through an endotracheal tube with positive end-expiratory pressure is indicated for severely hypoxic patients. Aspiration of bronchoalveolar lavage or charcoal hemoperfusion is useful at any stage of respiratory injury caused by SM¹⁹. Other commonly used treatment for SM-induced respiratory injury are given in Table 5.

4.4 General Precautions

In general, victims may suffer from dehydration as a result of extensive SM-induced skin burns and fluid accumulation in edematous

Table 4. Treatment for skin effects of SM exposure

Symptoms	Treatment
Contaminated skin	Decontamination
Persistent itching and severe erythema	Compound calamine lotion or petroleum jelly
Disinfectants	Chlorhexidine hydrochloride (0.5 %) or povidone-iodine containing soap
Severe itching in the genital area	Xylocaine or prilocaine, or corticosteroids like flumethasone and triamcinolone. Systemic analgesics like paracetamol, pethidine and morphine and antihistamines like clemastin or promethacene
Mustard blisters	Sterile petroleum jelly and povidone-iodine ointment
Secondary infection	Antibacterial drug, locally or systemically

tissues. Although, fluid requirements are generally less than thermal burns, intravenous solutions were used for all patients daily by monitoring blood fluid balance and serum electrolytes concentration¹⁷

Table 5. Treatment for respiratory tract effects of SM

Symptoms	Treatment
Mild injury	Treatment not required
Cough	Codeine
Pharyngitis	Alkaline gargle
Nasal irritation	Eye and nose drops
Severe respiratory tract injury	Antibacterial drugs
Laryngitis and tracheitis	Steam inhalation
Restlessness	Sedation by morphine or barbiturates
Other drugs	Acetyl cysteine, corticosteroid spray, aminophylline, theophylline, terbutaline, dextromethorphan with ammonium chloride
Severe exposure	Tracheostomy to relieve pharyngeal obstruction due to pseudomembranes or mechanical cleaning

Table 6. Drugs and chemicals tested against toxic effects of SM

Drugs or chemicals	References
Anti-inflammatory agents	
Dexamethasone	27
Betamethasone	23
Promethazine	27
Prednisolone	28
Hydrocortisone	9
Cortisone	9
Anti-oxidants and inhibitors of lipid peroxidation	
Vitamin-A	12,29
Vitamin-C	12,29
Vitamin-E	12,27,29
Hydroxyethyl rutoside	12,29
Gossypin	12,29
Sulphur mustard scavengers	
Sodium thiosulphate	12,27,29-31
N-acetyl-L-cysteine	31,32
BAL	9,33
2-Aminoethylisothiurea (AET)	33
Disulfiram	33
Dimethylsulphoxide	33
Dithiocarbamates	34
Thiophosphonates	34
Sodium diethyl dithiophosphate	9
Sodium diethyl dithiocarbamate	9
2-Mercaptoethanol	33
Cysteine	34
Cystine	33
Radioprotectors (WR-2721, WR-3689, WR-638, etc.)	9,33
Inhibitors of cell death and promoters of cell survival	
Niacinamide	35,36
Nicotinamide	11,35
NAD	9
3-Aminobenzamide	11
3-Methoxybenzamide	11
Nicotinic acid	
Glutathione	
Calcium gluconate	37
Miscellaneous agents	
Sodium citrate	30
Heparin	27
Atropine sulphate	27, 37
Sodium ethanemonothiothiophosphonate	38
2-Aminoethanol	33
Salbutamol	28
Carbamazepine	28
Dithiothreitol	17
5 % Dextrose	39
Dextrose saline	39
Opioids	28
Allopurinol	9
Oxypurinol	9

Nutritive diet should be given to SM-exposed victims. Gastrointestinal problems were not generally found in SM-exposed victims. Mild problems like nausea, headache, etc., may be treated symptomatically and liberal use of systemic wide spectrum antibiotics and analgesics is also recommended. In massive exposure, SM may induce severe leukopenia and in this case whole blood transfusion or plasma expanders should be considered.

5. ANTIDOTES TO SULPHUR MUSTARD POISONING

There is no specific antidote against SM intoxication and also no pretreatment is available to avoid SM injuries. Several hypotheses have been proposed for SM toxicity and various treatments have been tried in experimental animals. But all the drugs and chemicals screened so far have given only limited protection and there is no satisfactory antidote for SM toxicity. Drugs and chemicals screened for their antidotal efficacy against SM are listed in Table 6.

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