REVIEW

Clinical management of casualties exposed to lung damaging agents: a critical review

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There is no specific antidote for the treatment of casualties exposed to chlorine, phosgene, or mustards; therefore, management is largely supportive. Corticosteroid treatment has been given to casualties accidentally exposed to chlorine. Clinical data on efficacy are inconclusive as the numbers given steroids have been small and the indications for administration unclear. There have been no clinical controlled studies. There is a stronger evidence base from animal studies, particularly from porcine and rodent models. Lung injury induced by phosgene and mustard appears to be mediated by glutathione depletion, lipid peroxidation, free radical generation, and subsequent cellular toxicity. There is limited evidence to suggest that repletion of glutathione reduces and/or prevents lung damage by these agents. This may provide an opportunity for therapeutic intervention.

Lung damaging agents (LDAs) may be defined as chemicals that following inhalation induces pathological changes in the lung resulting in respiratory difficulty. As these compounds are invariably gaseous or volatile at ambient temperature and pressure, accidental or deliberate release is potentially capable of exposing large numbers of individuals to a toxic plume; therefore, there is the possibility of mass casualties.

This physicochemical property of LDAs has long been recognised—as illustrated by the fact that many such agents have been used as chemical warfare agents. However, as such agents are relatively easy to synthesise, or are used extensively in industry in developed countries, it is conceivable that they could be used as chemical weapons by terrorist groups against civilian populations.

This review focuses on the ''dual use'' chemicals, chlorine and phosgene, and the chemical warfare agent, mustard, and the available evidence on treatment regimes.

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METHODS

Information about chlorine, phosgene, and mustard was obtained by searching Medline, Embase, and PubMed from 1966 to October 2003, using key words: ''*chlorine*'', ''*chlorine poisoning*'', ''*chemical incidents*'', ''*phosgene*'', ''*mustard*'', and ''*mustard gas*'', and subsequently combined with the secondary keywords: ''*medical management*'', ''*clinical management*,'' *management*, ''*steroids*'', or ''*treatment*''. This search was supplemented by the use of the web based National Poisons Information Service information source ''Toxbase''.[1]

RESULTS

A Medline search for articles related to ''chlorine'' revealed 5784 hits, which following the application of the aforementioned secondary keywords yielded seven articles. Similarly, Embase revealed 2881 articles on chlorine, of which a further one was of interest. Toxbase yielded a further 12 relevant articles. For ''phosgene'', Medline revealed 254 articles (26 relevant), Embase 255 (two further articles) and PubMed (two articles). Toxbase yielded a further three articles of interest. A literature search for ''mustard'' revealed 5331 articles (13 relevant), Embase (four articles) and Toxbase a further one article.

Chlorine

Chlorine is a yellow-green gas at room temperature and pressure with a pungent, irritating odour. Being denser than air, it tends to accumulate at ground level. It is an extremely common agent of considerable commercial importance and is used extensively in the production of chlorinated organic polymers, solvents, and other organic chemicals.[2]

It was the first chemical to be used as a warfare agent during the first world war: released by German Forces on 22 April 1915. The line was being held by the First Canadian Division, which bore the brunt of the casualties, resulting in several cases of ''irritable heart'', bronchitis, ''gastric symptoms'', haemoptysis, asthma, and ''neuroses''.[3]

It is now recognised that acute exposure to chlorine causes symptoms of mucus membrane irritation, cough, haemoptysis, chest tightness, and dyspnoea. Physical examination following exposure to high concentrations may reveal tachypnoea, hypoxia, and wheezing.[2 4]

There are several reports of accidental exposure to chlorine in the literature and subsequent clinical management. Andelson and Kaufman described a 29 year old man and his 27 year old wife who were accidentally exposed to chlorine in their home. Both presented with respiratory distress, cyanosis, and hypotension. Despite receiving supplemental oxygen (100%),

Abbreviations: DBcAMP, dibutyryl adenosine 3′5′-cyclic monophosphate; ETYA, 5,8,11,4-eicosatetraynoic acid; GSH, glutathione; LDA, lung damaging agent; NAC, N-acetyl cysteine

prednisone, and penicillin, both patients died. The concentration of chlorine exposed to in these cases is unknown in this small study and the only conclusion that can be drawn is that both patients died despite intervention.[5]

In a similar study, two sisters were exposed to an unspecified dose of chlorine following an accident. Case 1 presented with a severe cough and chest pain. A chest *x* ray revealed bilateral pulmonary infiltrates; supplemental oxygen was given and the patient discharged a few days later. Spirometry at one year was consistent with both obstructive and restrictive airways dysfunction. Case 2 supposedly received similar exposure and presented with mucosal irritation, hoarseness, dyspnoea, and coughing. Supplemental oxygen and hydrocortisone 100 mg intravenously followed by prednisone 60 mg orally at 8 hours was given. The patient subsequently improved and was discharged. Spirometry was reported to be normal at one year.[6]

This is again a small, non controlled, study, making it difficult to ascertain the efficacy of the treatment regime. In addition, it may be that case 2 received a lower exposure than her sister, which would also explain the more favourable outcome.

Following a laboratory accident, two teenage children were exposed to chlorine. One casualty received a bronchodilator, frusemide, and dexamethasone, whereas the other received ''corticosteroids'' only.[7] Again, assessing the efficacy of treatment is extremely difficult.

There have also been a number of chemical incidents involving chlorine release reported in the literature. Following the accidental release of 300 litres of chlorine in Zaragosa, Spain, in 1981, 164 people required symptomatic treatment for nasal-pharyngeal pruritis, chest pain, tachypnoea, dyspnoea, headache, nausea, and vomiting, and two individuals presented with loss of consciousness. Supplemental oxygen and methylprednisolone 1 $mg \cdot kg^{-1}$ were administered symptomatically. A follow up study at 5 years revealed no persistent symptoms. The criteria for administration of treatment are not clear and thus the efficacy of treatment cannot be ascertained.[8]

Similar limitations apply to a report of 13 children presenting to an accident and emergency department following exposure to chlorine at a swimming pool. Again, treatment regimes varied, with all receiving humidified oxygen and a bronchodilator, with four receiving methylprednisone.[9]

Chronic exposure to chlorine has been investigated in construction workers with a confirmed diagnosis of reactive airways dysfunction syndrome. A questionnaire distributed to 71 such workers revealed that 58 had persistent respiratory symptoms and that four had received corticosteroid treatment. However, some of the patients in this study had a previous history of non-occupational asthma, which makes the interpretation of the data difficult.[10]

The use of animal models has allowed quantifiable chlorine concentrations to be applied under carefully controlled conditions and for treatment regimes to be scrutinised. In one such study, eighteen premedicated and anesthetised pigs were subjected to 140 ppm of chlorine gas for 10 minutes. The treatment group (beclomethasone dipropionate) had significantly higher $Pa0_2$ and higher ventilation to perfusion ratio and less histological damage than the control group.[11]

A similar study exposed 24 anesthetised juvenile female pigs to a higher concentration of chlorine—namely 400 ppm for 10 minutes. Likewise, steroid intervention (budesonide 0.1 $mg \cdot kg^{-1}$) given within 30 minutes of exposure was associated with more favourable cardiorespiratory symptoms and lower wet lung weights at autopsy.[12]

These studies support a protective role for corticosteroid intervention following experimental chlorine injury—at least in pigs. It is recognised, however, that the exposure of anesthetised pigs under controlled experimental conditions differs markedly from the likely exposure of casualties to chlorine either following an industrial accident or a deliberate release scenario.

The findings in pigs are supported by studies in rats exposed to 1500 ppm chlorine for 5 minutes. The dexamethasone treated group revealed significantly reduced pulmonary airway resistance and methacholine induced bronchoconstriction compared to the control group.[13]

Treatment of chemically contaminated casualties is discussed below.

Phosgene

Phosgene is a colourless gas at room temperature and pressure. It has a boiling point of 8.2℃, which makes it extremely volatile at room temperature. Initial exposure results in immediate coughing and choking, headache, lachrymation, tightness in the chest, and occasional nausea and vomiting. This is frequently followed by a period of 2–24 hours during which the patient appears well and symptom free. This period is typically followed by coughing, dyspnoea, tachypnoea, and cyanosis as a consequence of phosgene induced increase in alveolar pulmonary capillary permeability resulting in pulmonary oedema.[14] This may be precipitated by exercise as was frequently reported in the first world war.[15] The prognosis is good if casualties survive more than 48 hours.[16]

Phosgene was first synthesised by Davy in 1812, but prepared as a chemical weapon by Haber during the first world war; it was first used by German Forces on 19 December 1915 when 88 tons were released, which resulted in 1069 casualties and 120 deaths. It was subsequently utilised by the allies and accounted for 85% of all deaths attributed to chemical warfare during this campaign.[17]

Phosgene is also used industrially in organic synthesis, dye manufacture, in pharmaceuticals, agro-chemicals, synthetic foams, resins, and polymers. It is, therefore, readily available and, coupled to its recognised toxicity, is a suitable chemical warfare agent.

Again, there is no specific antidote for phosgene exposure and treatment is supportive, including evaluation of the airway, administration of supplemental oxygen, bronchodilators, adrenaline for children with stridor and dopamine for hypotension, bradycardia, and renal impairment.[4] Codeine phosphate may be beneficial for phosgene induced coughing at lower dosages; higher dosages may exacerbate respiratory depression.[17] Steroid treatment in phosgene exposure remains unproven.[18]

Phosgene induced pulmonary oedema has been investigated in buffer perfused isolated rabbit lungs, where it was shown to increase wet lung weight compared to controls. As this occurred independently of changes in right left atrial pressure, it implies that the oedema is a reflection of an increase in capillary permeability as opposed to altered haemodynamics. This is supported by the fact that phosgene exposure significantly increased the leakage of ^{125}I albumin compared to controls. Pretreatment with dibutyryl adenosine 3′5′-cyclic monophosphate (DBcAMP), aminophylline, or terbutaline plus isoproterenol effectively prevented the increase in lung weight and permeability induced by phosgene. Post treatment (within 10 minutes) with aminophylline and terbutaline also prevented the increase in lung weight. As the effects of DBcAMP and the β2 agonists, terbutaline and isoproterenol, are mediated by increasing intracellular cAMP levels, this would suggest a role for this mediator in preventing the cellular damage induced by phosgene.[19]

As phosgene is capable of reacting with cellular sulphydryl groups, reduced glutathione (GSH) redox state, and increased arachidonic acid mediator production and lipid peroxidation occur.[20] Several workers, therefore, have focused on the use of non-steroidal anti-inflammatory drugs and on agents increasing cellular GSH levels as a means of preventing lipid peroxidation induced pulmonary oedema.

Rats exposed to phosgene significantly decreased lung wet weight when given ibuprofen both prior to and after exposure, which suggests less oedema fluid,[21] whereas dietary administration of low dosages of the anti-oxidant n-propyl gallate significantly increases survival time in phosgene exposed mice.[22]

Sciuto *et al* investigated the effect of N-acetyl cysteine (NAC) on anaesthetised male New Zealand rabbits exposed to 1500 ppm of phosgene. Compared to animals treated with phosgene alone, NAC treated rabbits had significantly smaller increases in pulmonary wet weight, lower leucotriene levels, and higher GSH levels. This suggests that NAC may protect against phosgene induced pulmonary oedema by maintaining GSH levels and inhibiting production of inflammatory leucotrienes.[23]

Sciuto *et al* also investigated the protective effect of butylated hydroxyanisole pretreatment on phosgene induced pulmonary oedema under controlled conditions. Butylated hydroxyanisole was found to significantly prolong survival, lung GSH levels, and to significantly reduce pulmonary wet weight with respect to controls.[18] As pretreatment is an unlikely option for the treatment of casualties subjected to a deliberate release scenario, the data must be interpreted with caution.

Postexposure administration of a GSH repleting agent has been investigated in anaesthetised guinea pigs. It was found that intra-peritoneal administration of 5,8,11,14-eicosatetraynoic acid (ETYA) 5 minutes after exposure to phosgene at 44 ppm prevented GSH depletion and significantly reduced the lung wet weight:dry weight ratio as compared to a group that received phosgene only.[24] It is to be noted that only 5 minutes elapsed between exposure to phosgene and the administration of ETYA; such a short delay between exposure and administration is unlikely to be met in exposed casualties. The effect of longer time delays between exposure and administration would be more meaningful.

Mustard compounds

At room temperature, sulfur mustard is a yellow oily volatile liquid with a faint odour of garlic. It is a powerful vesicant resulting in erythema and subsequent formation of large fluid filled blisters. Inhalation of vapour may result in bronchitis, necrosis of the respiratory epithelium, and bronchopneumonia. As is the case for chlorine and phosgene, there is no specific antidote for mustard. The mainstay of management, therefore, is based upon physiotherapy, oxygen supplementation, antibiotics, and mechanical ventilation.[25]

Reports of managing mustard casualties during the Iran–Iraq conflict in the 1980s reveal that casualties were treated with high dosage prednisone (40–60 mg per day) broad spectrum antibiotics, and salbutamol orally (2 mg three times daily). Five such casualties were transferred to the United Kingdom, presenting with cough productive of sputum, inspiratory crackles, air flow limitation, and hypoxaemia. Steroid treatment was discontinued in all patients, while respiratory infections were appropriately treated with antibiotics; nebulised bronchodilators were ineffectual. Interestingly, it was reported that all five causalities had remarkable, if not complete, recovery of lung function.[26] This is encouraging, but it is not possible to ascertain whether this was because of one or all of the pharmaceutical interventions instigated as the treatment was not part of a clinical trial.

Several workers have investigated the ability of drugs to prevent sulfur mustard induced pulmonary injury. The GSH dependent detoxification of sulfur mustard in particular has been investigated.

Accordingly, NAC has been reported to prevent increased biochemical parameters in lavage fluid following exposure of anaesthetised rats to sulfur mustard. Thus, LDH, GGT, and albumin levels did not vary significantly from control values at 12 hours, which suggests reduction of cellular injury and transudation. Although this study is encouraging, it should be noted that NAC was co-administered with sulfur mustard and this again is an unlikely time frame for exposed casualties.[27] Indeed, several studies have demonstrated a beneficial effect of NAC when pre-administered in large dosages, but no such effect when administered postexposure.[28–30] By contrast, however, exposure of rat lung slices to benzenethiols (mustard scavengers) and cysteine esters (converts to GSH) did not produce a protective effect.[28]

In a study on a human bronchial-epithelium cell line (16HBE14o-) it was found that NAC and L-thiocitrulline (an L-arginine analogue) prevented sulfur and nitrogen-mustard induced cellular injury, as determined by a cytological colourimetric assay. More effective protection against sulfur mustard was provided by a drug combination, including L-thiocitrulline, NAC, the antioxidant dimethylthiourea, the nucleophile hexamethylenetetramine, and the anti-gelatinase doxycycline (DOX).[31] It is noteworthy that both doxycycline and NAC are already used in clinical practice and thus could be used to treat mustard contaminated casualties.

RECOMMENDATIONS FOR THE MANAGEMENT OF CASUALTIES

Exposure

Remove the patient as quickly as possible as a vital first aid measure. This may be accomplished by removing the casualty from the hazardous environment or by protecting the airway with a respirator. Contaminated clothing should be removed, decontamination undertaken as soon as possible, and the casualty provided with modesty clothing. As chlorine, phosgene, and mustard are highly chemically reactive, the reaction pathway is of the order of a few millimetres and thus exhalation is minimal; therefore, off-gassing is unlikely.

Airway

Secretions present in the airways of casualties are usually copious and watery. They may serve as an index to the severity of pulmonary oedema and do not require specific treatment, apart from suctioning and drainage to maintain a patent airway. Establishing an airway is crucial in a casualty showing hoarseness of the voice or stridor; such individuals may face impending laryngeal spasm and require intubation. Establishing a clear airway also minimises the work of breathing

Breathing

An elevation of the partial pressure of carbon dioxide (pCO_2) of greater than 45 mmHg is indicative of bronchospasm and, in such cases, the aggressive use of bronchodilators is indicated. Bronchospasm may occur in individuals with reactive airways and these patients should be given beta-adrenergic bronchodilators; their use is unlikely to compromise other pharmacological interventions. Parenteral administration of steroids (methylprednisolone) may also be indicated if bronchospasm is severe.

Positive airway pressure provides some control over the clinical complications of pulmonary oedema and the early use of a positive pressure mask may be beneficial. Pulmonary

oedema noted after a toxic inhalant exposure should be treated similarly to acute respiratory distress syndrome or non-cardiogenic pulmonary oedema. The early application of intermittent positive pressure ventilation (or positive end expiratory pressure ventilation at low tidal pressure) is desirable as this will delay or reduce the severity of resulting oedema. The use of diuretic drugs in this situation is of limited value; however, if diuretics are used, it is useful to monitor their effect by means of the pulmonary artery wedge pressure measurement because excessive use of diuretics may result in hypotension if positive end expiratory pressure ventilation is applied.

Oxygen treatment is definitely indicated and may require supplemental positive airway pressure to achieve inspired oxygen fractions (FiO_2) of 0.3–1.0 (30–100%). Intubation with or without ventilatory assistance may be required, and positive pressure may need to be applied during at least the end expiratory phase of the ventilation cycle. As chlorine, phosgene, and mustard are highly chemically reactive, the reaction pathway is of the order of a few millimetres and thus exhalation is minimal; therefore, off-gassing is not an issue.

Circulation

Cardiorespiratory resuscitation should be undertaken as appropriate. Accurate determination of a casualty's circulatory status is vital not just initially but also at regularly repeated intervals and whenever indicated by the clinical situation. Careful replacement of the intravascular volume is required to maintain haemodynamic stability.

Enforce rest. Even minimal physical exertion may shorten the clinical latent period and increase the severity of respiratory symptoms. Overt physical activity in a symptomatic case may precipitate acute clinical deterioration and even death. Strict limitation of activity by forced bed rest is mandatory for casualties with suspected pulmonary oedema. This applies equally to casualties irrespective of whether or not they have respiratory symptoms and whether or not there is objective evidence of pulmonary oedema.

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