

DEPARTMENT OF HEALTH

**EXPERT GROUP ON THE MANAGEMENT OF CHEMICAL
CASUALTIES CAUSED BY TERRORIST ACTIVITY**

FIRST REPORT

**TREATMENT OF POISONING BY
SELECTED CHEMICAL COMPOUNDS
OCTOBER 2003**

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CHAPTER 1

EXECUTIVE SUMMARY

1.1 The Expert Group on Management of Chemical Casualties Caused by Terrorist Activity (EGMCCT) was established to provide rapid advice to the Chief Medical Officer on the medical management of patients exposed to toxic chemicals as the result of terrorist incidents. An explanation of the way of working of the Group is provided in the Introduction (Chapter 1) of this report.

1.2 Four problems have been addressed to date. This summary provides short accounts of the Group's findings.

(i) *Use of oximes in nerve agent poisoning*

1.3 Nerve agents are organophosphorus compounds, which act by inhibiting the enzyme acetylcholinesterase. This results in the accumulation of acetylcholine at synapses, parasympathetic effector sites and neuromuscular junctions. The enzyme can, in some situations, be reactivated by the use of pyridinium oximes. These mono or bispyridinium compounds bind to the nerve agent-enzyme complex and cause the latter to be hydrolyzed. The effectiveness of oximes is dependent upon the exact nerve agent compound that has been bound to the enzyme, for example, the oxime pralidoxime mesilate is effective in sarin (GB) and VX poisoning but less so in tabun (GA) or cyclosarin (GF) poisoning. Furthermore, a secondary irreversible reaction described as aging of the nerve agent-enzyme complex, renders the complex refractory to oxime reactivation. Aging occurs very rapidly in the case of GD (soman) but more slowly with other nerve agents.

1.4 A number of oximes are available. The pralidoxime salts (including the chloride, methanesulfonate known as the mesilate, and the methyl sulphate) are perhaps the best known. Obidoxime (Toxogonin) is used in some countries but the H (Hagedorn) oximes are not yet in general use.

1.5 It is probable that the claim that asoxime chloride (HI-6) can reactivate soman-inhibited enzyme only applies to unaged enzyme and there is no unequivocal evidence of reactivation of aged soman-inhibited acetylcholinesterase by any oxime in any species *in vivo*. However, other pharmacological effects of HI-6, may be important after aging of the agent-enzyme complex is established. Therefore, HI-6 may still have some advantage in soman poisoning. It is recommended that a supply of HI-6 should be procured for this purpose.

1.6 With the possible exception of the treatment of soman and cyclosarin, when HI-6 might be preferred, a review of available experimental evidence suggests that there are no clinically important differences between pralidoxime, obidoxime and HI-6 in the treatment of nerve agent poisoning, if studies employing pre-treatment with pyridostigmine and/or prophylactic administration of oxime are excluded. In practice it is unlikely that the identity

of the nerve agent to which people are exposed will be known. It is recommended, therefore, that all nerve agent casualties should receive pralidoxime mesilate initially, and preferably prior to admission to hospital.

1.7 In the case of cyclosarin and soman poisoning, consideration should be given to the hospital use of HI-6, once supplies become available. It is recommended that HI-6 be obtained now for this purpose.

1.8 Whilst we recognise that it will be difficult to initiate treatment soon after poisoning in the setting of a terrorist incident, we believe that the acquisition and use of autoinjection devices, such as the ComboPen, would help. For the hospital setting we recommend that pralidoxime mesilate remains the oxime of choice in the UK, though we accept that HI-6 may be a better choice in cases of soman and cyclosarin poisoning. Thus we recommend that a supply of HI-6 be procured now for this purpose. Further research into the mode of action of H oximes and into alternative approaches to the treatment of nerve agent casualties is needed: research recommendations are provided in Chapter 7.

1.9 In the medium term, it is recommended that HI-6 should eventually replace pralidoxime mesilate for the treatment of nerve agent poisoning, at least in a civilian context.

1.10 Although we have been asked to focus on oximes we feel it important to stress the importance of atropine and, if necessary, assisted ventilation with supplementary oxygen and airway management in the early management of nerve agent casualties.

(ii) *Use of antidotes in treatment of poisoning by hydrogen cyanide*

1.11 Hydrogen cyanide, like all cyanide compounds, acts by binding to cytochrome enzymes and blocking the electron transport chain in mitochondria. Inhalation of hydrogen cyanide produces more rapid effects than ingestion of cyanide salts, such as potassium cyanide, and for treatment to be effective it must be given very rapidly following poisoning. In cases of ingestion of cyanide salts or of extensive skin contamination an interval between exposure and the onset of very severe effects may occur. Delayed therapy in such cases can be effective; this is unlikely to be the case in patients exposed to hydrogen cyanide.

1.12 A number of approaches to the treatment of cyanide poisoning have been developed. Each depends, at least initially, upon the binding of cyanide ions to produce a non-toxic complex. Binding can be achieved with cobalt ions or by reaction with iron in methaemoglobin to produce cyanmethaemoglobin. Dicobalt edetate (a chelate of cobalt ions) contains some free cobalt ions and it is probable that both dicobalt edetate and the free cobalt ions bind cyanide, but free cobalt is itself toxic and, in the absence of cyanide, may produce significant adverse effects. Intravenous glucose is given to oppose these effects. In the case of proven cyanide poisoning the

administration of glucose, in addition to dicobalt edetate has been found to be unnecessary, but glucose is generally given as a precautionary measure.

1.13 It is stressed that therapy must be given as rapidly as possible after poisoning and it is accepted that this may be difficult in cases of exposure to hydrogen cyanide poisoning resulting from terrorist activity. It is, in our view, unlikely that those most in need of therapy could be treated sufficiently quickly to save their lives and that the great majority of those surviving the initial exposure and reaching the point at which therapy could be given, will not benefit from such treatment. Despite this conclusion we appreciate that a minority of patients reaching clinical care may still benefit from therapy.

1.14 The Department of Health has stockpiled dicobalt edetate and we support this approach. In our view, dicobalt edetate, given intravenously, is likely to lead to more rapid binding of cyanide ions than the main alternative: the production of methaemoglobin by sodium nitrite. We have examined the case for use of hydroxocobalamin and find it less well supported in cases of exposure of hydrogen cyanide than that of dicobalt edetate.

1.15 We have also considered the need to provide assisted respiration and oxygen to casualties suffering from exposure to cyanide. There is some experimental evidence derived from studies in animals to support the use of oxygen. We therefore recommend that assisted ventilation and oxygen should be provided as soon after exposure to cyanide as possible.

1.16 Amyl nitrite provides the only form of treatment for cyanide poisoning that need not be given intravenously. However, we think that the generation of useful amounts of methaemoglobin by any possible means of providing amyl nitrite is unlikely and we do not recommend that this approach be pursued.

(iii) *Treatment of patients exposed to lung damaging compounds*

1.17 A large number of chemicals can, if inhaled, damage the lung. These include the early chemical warfare agents chlorine and phosgene, and a number of comparatively common industrial chemicals. Exposure to such compounds produces inflammation of the conducting airways and of the delicate tissues of the gas exchange zone of the lung. This causes bronchoconstriction and pulmonary oedema. No specific antidotes are known. However, bronchodilator substances, as used in the management of asthma, can be useful in reversing bronchoconstriction. The use of corticosteroids, in the management of chemically induced pneumonitis and pulmonary oedema, remains controversial and we have not been able to discover strong evidence to suggest that parenteral administration of steroids should be recommended. The use of inhaled steroids is not likely to be associated with the side effects that may accompany the parenteral use of high dose steroids and may be useful in treating bronchial reactions.

1.18 As in cases of nerve agent or cyanide exposure, early access to assisted ventilation and oxygen may be needed.

(iv) *Acute management of mustard gas-induced eye injuries*

1.19 Sulphur mustard is an oily liquid that gives off a vapour which on contact with the skin produces blisters: the liquid and the vapour are described as vesicants. Both liquid and vapour can produce severe damage to the eyes though this tends to be limited to the anterior part of the eye: conjunctiva, cornea and, sometimes, the iris, the deeper parts of the eye seldom being affected. Rapid removal of any liquid contamination of the eye by irrigation with copious amounts of water is essential: any delay will significantly reduce the effectiveness of irrigation as mustard binds rapidly to protein thus becoming impossible to remove. Exposure to vapour produces a delayed but severe inflammatory reaction and all treatment is essentially palliative. Eye injuries caused by mustard gas should be managed by ophthalmologists: a range of therapeutic substances may be used and details are provided in this report though the evidence base for their efficacy is scant. It is important to recall that there is no specific antidote for mustard gas and no known way of reversing the effects of mustard gas on tissues.

1.20 A short note outlining the general principles of management of casualties contaminated by chemical compounds has been provided as Annex 1. This note sets out a modification of the standard ABC approach.

1.21 Research recommendations are made in Chapter 7.

CHAPTER 2

INTRODUCTION

2.1 The Expert Group on Management of Chemical Casualties Caused by Terrorist Activity (EGMCCT) was established in September 2002 on an *ad hoc* basis to provide advice to the Chief Medical Officer. The Group was asked to provide advice on the clinical management of patients exposed to toxic chemicals as a result of terrorist activity. An initial list of chemicals of concern to the Department of Health was drawn up by officials and considered by the Members of the Group.

2.2 Members accepted that detailed advice was required and, further, that this should be based as far as possible on a systematic examination of the relevant evidence. It was noted that though much relevant information was available in the unclassified literature, some classified material would need to be examined. The Group agreed that it was likely and desirable that their reports would not contain classified material and argued that the reports should be published in such a way that as large an audience as possible could be provided with the Group's views.

2.3 It was accepted that a rapid response was needed and Members were encouraged to use their expert judgement in coming to a considered view based on the available literature. Some problems have been studied in depth in many countries and both the classified and unclassified literature is extensive; other problems have received comparatively little attention, at least little appears to have been published. This and the need for a rapid response has led to the short reports not being identical in format: some are presented as a series of key points with limited discussion, others in a comparatively discursive format.

2.4 In discussing ways of working, Members felt that publication of short reports on the Department of Health website (www.doh.gov.uk) would be appropriate. Where possible, more detailed reports giving as much supporting evidence as possible should be published in the peer-reviewed literature. This approach has been followed and a detailed review of oximes is currently being prepared for publication.

2.5 Members have been asked to advise on further compounds and problems that need to be addressed. Ricin and irritant incapacitants have been suggested and will be considered in the next report. Advice on the provision of oxygen and respiratory support as rapidly as possible after exposure to toxic substances will also be provided. A small working group to look at this has been established.

2.6 Members have also been asked to advise on what research is needed to support their recommendations regarding the medical management protocols. These recommendations are included in the accounts of individual problems and collated at the end of the report.

2.7 The Department of Health is grateful to Members of the Expert Group for the effort they have put into preparing this first report in such a short time.

CHAPTER 3

USE OF OXIMES IN NERVE AGENT POISONING

3.1 Nerve agents are organophosphorus compounds that bind to acetylcholinesterase (AChE) and result in the accumulation of acetylcholine at synapses, parasympathetic effector sites and neuromuscular junctions. The effects of acetylcholine can be, in part, blocked by atropine and AChE reactivated, in some cases, by the use of pyridinium oximes. The case for the rapid administration of atropine and the provision of supported ventilation, preferably with oxygen enriched air, is beyond dispute. A number of oximes exist and we have focused, here, on this aspect of therapy.

3.2 An important difference between on-target military attacks against relatively well-protected armed forces and nerve agent attacks initiated by terrorists against a relatively unprotected civilian population is the time after exposure when specific therapy is first administered. In a civilian context, even conservative estimates suggest a delay of 10-20 minutes between symptomatic exposure and the first administration of atropine/oxime. In worst case scenarios this time delay may be in excess of 30 minutes.

Review of the literature

3.3 All available open literature has been reviewed and, in addition, access to relevant documentation at DSTL Porton Down has been provided.

3.4 Experimental studies on the treatment of nerve agent poisoning have to be interpreted with caution for several reasons. Antidotal studies in animals have to be designed with great care or they may demonstrate the efficacy of antidotes in circumstances that do not occur in civilian clinical practice. Thus, some studies have used prophylactic protocols, whereas the drugs concerned (atropine, oxime, diazepam) would only be given to a civilian population *after* exposure. The experimental use of pyridostigmine before nerve agent exposure, though rational, is not of relevance in the civilian context. Hence, these studies are difficult to interpret in relation to post-exposure treatment. Even those experimental studies in which antidotes have been administered after nerve agent dosing are not beyond reproach. In many studies antidotes were administered within a few minutes of, or even immediately after, exposure.

3.5 Specific issues considered were:

- (i) The clinical relevance of the species employed in experimental studies, particularly in relation to rates of ageing of the AChE enzyme in soman poisoning;
- (ii) The time relationship between exposure and treatment in experimental studies, including the impact of pre-treatment.

3.6 It has been assumed generally that monkeys would be a reasonable model for humans and it has been stated (Inns and Leadbeater, 1983; Leadbeater *et al.*, 1985) that guinea pigs are also good models for humans. This was on the basis of similarity of protection ratios achieved for the treatment of soman-poisoned rhesus monkeys with atropine and oxime as compared with similarly poisoned and treated guinea pigs.

3.7 There are, however, significant differences between the aging rates of the nerve agent-acetylcholinesterase complex depending both on the identity of the nerve agent and the animal species concerned. Aging of complexes involving soman is always much more rapid than that of complexes involving other nerve agents. In the case of soman-bound acetylcholinesterase the mean half life ($t_{1/2}$)¹ for aging in primates is 0.88-1.4 minutes, whilst in rodents and guinea pigs it is much longer: 7.6-8.6 minutes. The aging process is thus much slower in rodents and guinea pigs than in primates. The $t_{1/2}$ of the soman-erythrocyte acetylcholinesterase complex in man is short (1.3 minutes) as in other primates (i.e. aging of the complex in man is rapid). This leads us to think that the guinea pig would not be a good model for man in soman poisoning. Unfortunately, the studies performed by Inns and Leadbeater (1983) were not published in full and it is impossible to say why similar protection ratios were observed in primates and guinea pigs.

3.8 *In vitro* studies on human erythrocyte AChE have employed measures to prevent aging of the soman-inhibited complex. *In vivo* studies in rodents have employed protocols in which treatment was given before substantial ageing would have occurred. Neither approach can be used to predict successful reactivation of the aged soman-inhibited complex in humans. Hence, the results of such studies probably have little relevance to the management of human soman poisoning.

3.9 It is probable that the claim that HI-6 can reactivate soman-inhibited enzyme only applies to unaged enzyme and there is no unequivocal evidence of reactivation of aged soman-inhibited AChE by any oxime, in any species, *in vivo*. However, other pharmacological effects of some oximes (i.e. those not mediated by AChE reactivation), such as have been reported in the case of HI-6, may be important once aging of the agent-enzyme complex is established, and therefore HI-6 may have some advantage in soman poisoning. Although this has still to be confirmed, it is recommended, that a supply of HI-6 should be procured specifically for the treatment of soman and cyclosarin poisoning.

3.10 With the possible exception of the treatment of soman and cyclosarin, when HI-6 might be preferred, a review of available experimental evidence suggests that there are no clinically important differences between pralidoxime, obidoxime and HI-6 in the treatment of nerve agent poisoning, if studies employing pre-treatment with pyridostigmine are excluded. Moreover there is much more clinical experience of pralidoxime in UK than of any other oxime.

¹ Aging half-life, $t_{1/2}$: this is the time taken for 50% of the nerve agent-AchE complex to change to its aged form.

3.11 It is recommended, therefore, that all casualties should receive pralidoxime mesilate initially, and preferably prior to admission to hospital.

3.12 In the case of cyclosarin and soman poisoning, consideration should be given to the hospital use of HI-6, once supplies are available. It is recommended that a supply of HI-6 be obtained for this purpose.

3.13 In the medium term, it is recommended that HI-6 should eventually replace pralidoxime mesilate for the treatment of nerve agent poisoning, at least in the civilian context.

3.14 In experimental studies, a delay of even 12 minutes in the administration of oximes reduced the protection ratio (LD_{50} with treatment/ LD_{50} without treatment) substantially. It is therefore important that oximes are administered as soon as possible after exposure, even in the case of nerve agents other than soman (Green *et al.* unpublished observations).

Treatment of nerve agent poisoning outside hospital

3.15 Arrangements need to be in place to ensure that civilian casualties receive antidotal treatment as soon as possible after exposure. This is of particular importance in the case of soman poisoning, as aging of the soman-enzyme complex occurs very rapidly. However, as it is very unlikely that the identity of the nerve agent will be known with certainty before the admission of casualties to hospital, therefore, HI-6 does not need to be substituted for pralidoxime mesilate prior to hospital admission.

3.16 Civilian casualties who have been exposed to nerve agents and who have developed rhinorrhoea and bronchorrhoea should be given atropine as a matter of urgency. These casualties should also receive pralidoxime mesilate as soon as possible. This could be done most conveniently by the administration of the contents of an autoinjection device such as the ComboPen², intramuscularly. Severely intoxicated casualties may require the administration of the contents of up to three ComboPens at five fifteen-minute intervals prior to admission to hospital.

3.17 Children more than eight years of age who meet the criteria for treatment should be given the contents of one ComboPen, which may be repeated at 5-15 minute intervals. In the case of children less than eight years of age but more than 1 year old and who have features of systemic toxicity, atropine, 600 µg, should be administered initially, preferably intravenously. For those under 1 year of age a dose of 200 µg atropine should be used.

3.18 Pregnant women who have the features of systemic nerve agent toxicity should receive the same treatment regimen as other adults.

² Autoinjection devices, such as the ComboPen, generally contain 2 mg atropine, an oxime and, in some cases, a soluble form of diazepam (Avizafone)

3.19 Casualties who do not develop the features of systemic toxicity, notably rhinorrhoea and bronchorrhoea, should be triaged but not given atropine and/or pralidoxime.

Treatment of nerve agent poisoning in hospital

3.20 If rhinorrhoea or bronchorrhoea develops, atropine 2 mg in an adult (20 µg/kg in a child of less than 8 years of age) should be administered intravenously every 5-15 minutes until secretions are minimal and the patient is atropinized (dry skin and sinus tachycardia). In severe cases, repeated doses of atropine will be required.

3.21 Pralidoxime mesilate 30 mg/kg body weight intravenously every four to six hours should be administered to patients with systemic features of poisoning, and who require atropine, the duration of treatment depending on the clinical response, the presence of clinical features and the erythrocyte acetylcholinesterase activity. Alternatively, an infusion of pralidoxime mesilate 8-10 mg/kg/hr may be administered following an initial loading dose.

3.22 It is recommended that pralidoxime mesilate (or HI-6) should be administered for as long as atropine is indicated. For the majority of individuals this will be for less than 48 hours.

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CHAPTER 4

USE OF ANTIDOTES IN CYANIDE POISONING

4.1 Hydrogen cyanide (HCN) and cyanide salt exposure potentially leads to clinical effects within seconds or minutes after inhalation or ingestion, respectively. Initially giddiness, headache, anxiety, confusion and dyspnoea occur and may be rapidly followed by coma, convulsions, bradycardia, hypotension and metabolic acidosis. Exposure to HCN may be fatal within minutes. Ingestion of cyanide salts may also be rapidly fatal. HCN is a colourless gas with a distinct odour of bitter almonds. The threshold for odour detection of cyanide in humans is two to five parts per million. Olfactory fatigue is rapid and some 20% or more of the population may not detect HCN since this ability is genetically determined.

4.2 Hydrogen cyanide may be absorbed by inhalation, ingestion, and through the eye and skin. Cyanides inhibit cellular respiration by blocking electron transport at the cytochrome a_3 complex. This impairs mitochondrial oxidative metabolism. The clinical effects are primarily due to an inability to utilise oxygen, rather than tissue hypoxia. In massive cyanide poisoning other mechanisms may contribute to clinical effects such as pulmonary and coronary arterial vasoconstriction and impaired ventilation with decreased cardiac output. Cyanides act extremely quickly once absorbed. HCN inhalation can be lethal within seconds; ingestion of inorganic cyanide salts such as potassium or sodium cyanide may produce clinical effects within minutes and fatalities within hours. Dermal exposures to cyanides have resulted in fatalities.

Review of treatments

4.3 The treatment of hydrogen cyanide and cyanide salt poisoning is primarily supportive. It includes removal of the casualty from exposure, decontaminating where necessary and administration of high concentration oxygen. Support of ventilation and administration of oxygen are considered to be important aspects of treatment for severe poisoning.

4.4 There are, in addition, currently four cyanide antidotes available within the United Kingdom, though not all have licence authorisation for this specific use.

- Nitrites
- Dicobalt edetate
- Sodium thiosulphate
- Hydroxocobalamin

All these drugs have been recognised, and used as cyanide antidotes, for more than 40 years. A number of case reports testify to their clinical effectiveness with at times rapid and spectacular reversal of the cardiovascular and nervous system abnormalities induced by cyanide, even

hours after poisoning has occurred. However, there are differences in the efficacy and side effects of these antidotes.

Methaemoglobin Formers

4.5 Methaemoglobin formers include sodium nitrite, amyl nitrite and 4-dimethylaminophenol (DMAP). Concerns exist about the safety of sodium nitrite because of the potential to form excess methaemoglobin, which reduces the oxygen carrying capacity of the blood, causing possible further harm. Further uncertainty concerns the recommended concentrations of methaemoglobin that need to be generated (ranging from <10% to 40%), the difficulty in predicting methaemoglobin levels for any one individual, and the difficulties in measuring methaemoglobin in the pre-hospital setting and the Accident and Emergency department. There is individual variation in susceptibility to methaemoglobin-inducing agents. The optimum concentration of methaemoglobin required is likely to depend upon the severity of the cyanide poisoning.

4.6 Nitrites may also be inhaled in the form of amyl nitrite and this used to be part of a cyanide antidote kit. Amyl nitrite is now a controlled drug and pharmacies are no longer incorporating it into cyanide antidote kits. It does, however, have the advantage of ease of administration. Nitrites may cause hypotension, particularly if given too quickly

Dicobalt edetate

4.7 Commercial preparations of dicobalt edetate contain free cobalt ions. Cobalt ions are themselves toxic and thus administration of commercial preparations of dicobalt edetate in the absence of cyanide poisoning may lead to severe adverse effects. If cyanide ions are present these bind to the free cobalt ions and thus the toxic effects of both the cyanide ions and the free cobalt ions are mutually antagonised (i.e. the cobaltcyanide complex is much less toxic than its components). Both dicobalt edetate and free cobalt ions bind covalently to cyanide ions. The adverse effects seen when commercial preparations of dicobalt edetate are given in the absence of cyanide poisoning include hypotension, cardiac arrhythmias and facial and laryngeal oedema. These effects can be reduced by the administration of glucose. Glucose is often given with the commercial preparations of dicobalt edetate as a precautionary measure. Equipment for emergency endotracheal intubation should be immediately available if dicobalt edetate is given.

Sodium thiosulphate

4.8 This is an additional antidote that aids cyanide elimination but acts too slowly to be used alone. It is often given with the other cyanide antidotes as 50 ml of a 25% solution over 10 minutes. Sodium thiosulphate is recommended after methaemoglobin-producing cyanide antidotes.

Hydroxocobalamin

4.9 Hydroxocobalamin binds cyanide and high doses have been studied in both healthy volunteers and in fire victims. These studies suggest that hydroxocobalamin, in doses up to 15 grams, is tolerated well though data on efficacy are less clear. The need for the rapid intravenous administration of large volumes of this antidote makes its use difficult in a pre-hospital setting.

Discussion

4.10 Table 4.1 summarises antidotes for cyanide poisoning by agent, mechanism of action, route of treatment, dose required, concurrent treatment recommendations, administration time recommended, response time, potential antidote toxicity, and the shelf life of the antidote.

4.11 In the absence of clear information concerning the nature of exposure it is often difficult to diagnose cyanide poisoning. The absence of specific diagnostic features, together with, for example, many people presenting with decreased consciousness is suggestive, but not diagnostic of cyanide poisoning. Rapid clinical diagnosis may rely in part upon the response to a therapeutic challenge with an antidote. An antidote that is both safe and effective is therefore clearly preferable.

4.12 Due to its rapid action, inhalation of hydrogen cyanide may result in patients who are severely poisoned and may not survive to receive any antidote. Patients who are fully conscious and breathing spontaneously probably do not require any life saving antidote, as they will ultimately detoxify any cyanide themselves.

4.13 In the presence of a clear history of cyanide exposure, for example in an industrial setting, or the event of multiple deliberate releases where the agent has been identified from a previous release, use of a cyanide antidote in addition to oxygen may be justified. Unless ambulances routinely carry antidotes it is difficult to foresee circumstances where pre-hospital administration is likely to occur unless prior knowledge of an intent to release is available.

4.14 By relying upon clinical criteria to diagnose HCN toxicity some patients may be treated unnecessarily. Although effective, the toxicity of dicobalt edetate in the absence of cyanide poisoning limits its use in the pre-hospital setting and potentially even in an Accident and Emergency Department. In circumstances of clear, severe cyanide poisoning its inherent toxicity is less of an issue. Concerns for the safety of methaemoglobin formers such as nitrites and DMAP complicate their use where mass casualties are being managed and in cases of cyanide poisoning where carbon monoxide poisoning co-exists. Evidence exists for the safety of hydroxocobalamin in non-poisoned patients and in the management of HCN exposures, though large doses must be administered IV where poisoning is severe.

Recommendations

4.15 In cases of hydrogen cyanide inhalation the most important action fundamental to survival is removing the casualty from exposure and prevention of further absorption with decontamination. As long as the patient does not have severe clinical signs such as loss of consciousness or convulsions and the clinical condition is not deteriorating then supportive care with oxygen therapy may be sufficient. Issues surrounding the timely provision of all antidotes exist.

4.16 Any patient who is fully alert when they reach hospital (i.e. A on the AVPU scale) following hydrogen cyanide inhalation and who has been suitably decontaminated will only require observation and reassurance. However, those who arrive with an altered conscious level (i.e. VPU on the AVPU scale) may well require oxygen, ventilatory support and an antidote. Inevitably, decisions on specific treatment remain the responsibility of the clinician treating the patient.

Table 4.1 Summary of Antidotes for Cyanide Poisoning

Agent	Mechanism	Route	Dose	Concurrent drugs	Admin time	Potential antidote toxicity
Oxygen	Increased arterial O ₂ content, potentiates activity of other antidotes	Inhalation via mask or endotracheal tube (ETT)	High flow via mask or 100% via ETT	Oxygen used as primary antidote in all cases	No more than 24 hours	Unlikely – possible in patients with COPD
Amyl Nitrite	Methaemoglobin formation	Inhalation	Adults: 0.2 ml Paeds: 0.2 ml may need repeating	Oxygen (not simultaneously)	30 seconds per minute	Difficult to achieve effective antidotal levels without cardiovascular collapse
Sodium Nitrite	Methaemoglobin formation	Intravenous injection	Adults: 300 mg (10 ml of 30 mg/mL 3%) Paeds: 0.13-0.33 ml/kg of 30 mg/mL (3%) solution (ie 4 mg to 10 mg/kg body weight)	Adults: sodium thiosulphate 25 mL of 500 mg/mL, (50%) solution and oxygen Paeds: sodium thiosulphate 1.65 mL/kg body weight of 250 mg/mL (25%) solution (Approx 400 mg/kg body weight) and oxygen	No less than five minutes and up to 20 minutes	Methaemoglobinaemia, vasodilation and cardiovascular collapse
Dicobalt Edetate	Binding of cyanide ions by dicobalt edetate and by free cyanide ions	Intravenous injection	Adults: 300 mg (20 ml of 15 mg/mL (15%)) Paeds: 4-7.5 mg/kg (0.3-0.5 ml/kg of 15 mg/mL (15%))	50 ml Dextrose (500 g/L) IV immediately after each dose and oxygen	1 minute	Urticaria, oedema of face and neck, chest pains, dyspnoea, hypotension, convulsions
DMAP	Methaemoglobin formation	Intravenous injection	Adults: 3.25 mg/kg Paeds: 3.25 mg/kg	Oxygen and sodium thiosulphate	1 minute	Methaemoglobinaemia vasodilation and cardiovascular collapse, haemolysis, elevated bilirubin and iron (this is unlikely to be relevant to single dose exposure)
Hydroxocobalamin	Binds cyanide ions	Intravenous injection	Adults: 5-10 g Paeds: 70 mg/kg	5 g reconstituted in 100 ml 0.9% saline. Oxygen	20 minutes	Reddish discoloration to skin and mucous membranes
Sodium Thiosulphate	Sulphur donor for endogenous enzymatic conversion of cyanide to thiocyanate	Intravenous injection	Adults: sodium thio-sulphate 25 mL of 500 mg/mL (50%) solution and oxygen Paeds: sodium thio-sulphate 1.65 mL/kg body weight of 250 mg/mL (25%) solution (approx 400 mg/kg body weight) and oxygen	Oxygen and sodium nitrite OR Oxygen and DMAP	10 minutes	Excess administration may cause hypernatraemia

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CHAPTER 5

LUNG DAMAGING AGENTS

Chlorine

5.1 Chlorine is a yellow-green gas at room temperature and pressure with a pungent, irritating odour. It is denser than air, and tends to accumulate at ground level. Chlorine is an extremely common agent of considerable commercial importance, being used extensively in the production of chlorinated organic polymers, solvents and other organic chemicals.¹

5.2 Chlorine, the first chemical to be used as a warfare agent during the First World War, was released by German Forces in April 1915 at the Ypres salient. 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".²

5.3 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.^{1,3}

5.4 There is no specific antidote for chlorine exposure and management is largely supportive, involving evaluation and support of breathing and circulation, establishment of IV access, administration of supplemental oxygen, bronchodilators and standard treatment of coma, hypotension and seizures.⁴ Corticosteroids have also been given and their use is reviewed in the case studies below.

5.6 We think it is important to point out that in cases of significant lung injury caused by exposure to chlorine and other compounds, supported ventilation, preferably with supplementary oxygen, is of vital importance. Positive pressure ventilation is an established approach in such cases.

Case Studies

5.7 There are several reports of accidental exposure to chlorine in the literature. 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%), prednisone and penicillin, both patients died. The concentration of chlorine 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

5.8 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.

5.8 Case 2 allegedly received similar exposure and presented with mucosal irritation, hoarseness, dyspnoea and coughing. Supplemental oxygen and hydrocortisone 100mg IV followed by prednisone 60 mg orally at 8 hours were 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.

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

5.10 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 Saragossa, Spain, in 1981, 164 people required symptomatic treatment. This included supplemental oxygen and 1 mg Urbason/kg body weight. 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

5.11 Similar limitations apply to a report of thirteen children presenting to an Accident & Emergency department following exposure to chlorine at a swimming pool. Again, treatment regimes varied, with all receiving humidified oxygen and a bronchodilator, whilst only 4 received methylprednisolone⁹.

5.12 Chronic exposure to chlorine has been investigated in construction workers with a confirmed diagnosis of reactive airways dysfunction syndrome (RADS). A questionnaire distributed to 71 such workers revealed that 58 had persistent respiratory symptoms and that 4 had received corticosteroid treatment. However, some of the patients in this study had a previous history of non-occupational asthma, making the interpretation of the data difficult¹⁰.

5.13 The utilisation 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 pre-medicated and anaesthetised pigs were subjected to 140 ppm of chlorine gas for 10 minutes. The treatment group (beclomethasone dipropionate) had significantly higher PaO₂ and ventilation to perfusion ratio and less histological damage than the control group.¹¹

5.14 A similar study exposed 24 anaesthetised juvenile female pigs to a higher concentration of chlorine, namely 400 ppm for 10 minutes. Likewise, steroid intervention (budesonide 0.1 mg/kg) given within 30 minutes of

exposure was associated with more favourable cardio-respiratory symptoms and lower wet lung weights at autopsy.¹²

5.15 These studies support a protective role for corticosteroid intervention following experimental chlorine injury, at least in pigs. The exposure of anaesthetised pigs under controlled experimental conditions, however, differs markedly from the likely exposure of casualties to chlorine either following an industrial accident or a deliberate release scenario. Caution is therefore required in extrapolating the data to man.

5.16 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, as compared to the control group.¹³

Phosgene

5.17 Phosgene is a colourless gas at room temperature and pressure. It has a boiling point of 8.2°C, making it extremely volatile at room temperature. Initial exposure results in immediate coughing and choking, headache, lachrymation, tightness of the chest and nausea and vomiting. This is frequently followed by a period of 2-24 hours during which the patient appears well and symptom free. This is followed by coughing, dyspnoea, tachypnoea and cyanosis, as a consequence of a phosgene-induced increase in alveolar pulmonary capillary permeability, resulting in delayed pulmonary oedema. The prognosis is good if casualties survive more than 48 hours.¹⁴

5.18 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 the 19th December, 1915, when 88 tons were released, resulting in 1069 casualties and 120 deaths. Phosgene was subsequently utilised by the allies and accounted for 85% of all deaths attributed to chemical warfare during this campaign.¹⁵

5.19 Phosgene is also used in industry in organic synthesis, dye manufacture, in pharmaceuticals, agro-chemicals, synthetic foams, resins and polymers. It is therefore readily available and this, coupled to its recognised toxicity, makes it suitable for use as a terrorist chemical warfare agent.

5.20 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; high doses may exacerbate respiratory depression.¹⁴ Steroid therapy in phosgene exposure remains unproven.¹⁶

5.21 As phosgene is capable of reacting with cellular sulphydryl groups, reduce glutathione (GSH) redox state and increase arachidonic acid mediator production and lipid peroxidation,¹⁷ several workers have focused on agents

increasing cellular GSH levels as a means of preventing lipid peroxidation-induced pulmonary oedema.

5.22 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 leukotriene levels and higher glutathione levels. This suggests that NAC may protect against phosgene-induced pulmonary oedema by maintaining GSH levels and inhibiting production of inflammatory leukotrienes.¹⁸

5.23 This group of workers also investigated the protective effect of butylated hydroxyanisole (BHA) pre-treatment on phosgene-induced pulmonary oedema under controlled conditions. BHA was found to significantly prolong survival, raise lung GSH levels and to significantly reduce pulmonary wet weight with respect to controls.¹⁷ As pre-treatment is an unlikely option for the treatment of casualties subjected to a deliberate release scenario, the data must be interpreted with caution.

5.24 Post-exposure administration of a GSH-repleting agent has been investigated in anaesthetised guinea pigs. It was found that in administration of 5,8,11,14-eicosatetraenoic acid (ETYA) 5 minutes after exposure to phosgene at 44ppm prevented GSH depletion and significantly reduced the lung wet weight/dry weight ratio as compared to a group that received phosgene only.¹⁹ 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 have been more meaningful.

Mustard Gas

5.25 At room temperature, sulphur mustard is a yellow oily volatile liquid, with a faint odour of garlic. It is a powerful vesicant, resulting in erythema of the skin and subsequent formation of large fluid filled blisters. Inhalation of vapour may result in bronchitis, necrosis of the respiratory epithelium and broncho-pneumonia. There is no specific antidote for mustard. The mainstay of management is based upon physiotherapy, oxygen supplementation, antibiotics and mechanical ventilation.²⁰

5.26 Several workers, however, have investigated the ability of drugs to prevent sulphur mustard-induced pulmonary injury. The GSH-dependent detoxification of sulphur mustard in particular has been investigated.

5.27 NAC has been reported to prevent increases biochemical parameters in lavage fluid following exposure of anaesthetised rats to sulphur mustard. LDH, GGT and albumin levels did not vary significantly from control values at 12 hours, suggesting reduction of cellular injury and transudation. Although this study is encouraging, it should be noted that NAC was co-administered with sulphur mustard and this again is an unlikely time frame for exposed

casualties.²¹ By contrast, however, exposure of rat lung slices to benzenethiols (Mustard scavengers) and cysteine esters (GSH precursors) did not produce a protective effect.²²

5.28 In a study on a human bronchial-epithelium cell line (16HBE14o-), it was found that NAC and L-thiocitrulline (L-TC, a l-arginine analogue) prevented sulphur and nitrogen-mustard induced cellular injury, as determined by a cytological colourimetric assay. More effective protection against sulphur mustard was provided by a drug combination including L-TC, NAC, the antioxidant dimethylthiourea, the nucleophile hexamethylenetetramine and the anti-gelatinase antibiotic doxycycline (DOX).²³ It is noteworthy that both DOX and NAC are already available in clinical practice and thus could be used to treat mustard contaminated casualties.

Conclusions

5.29 There are no specific antidotes for the treatment of casualties exposed to chlorine, phosgene or mustards. Management is, therefore, supportive.

5.30 Cortico-steroid therapy has been given to casualties accidentally exposed to chlorine. Clinical data regarding efficacy are inconclusive, as the numbers given steroids have been small and the indications for administration unclear. There have been no controlled clinical studies. There is a stronger evidence base from animal studies, particularly from porcine and rodent models.

5.31 Lung Injury induced by phosgene and mustard appears to be mediated by GSH depletion, lipid peroxidation, free radical generation and subsequent cellular toxicity. There is limited evidence to suggest that repletion of GSH reduces and/or prevents lung damage by these agents.

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CHAPTER 6

ACUTE MANAGEMENT OF MUSTARD GAS* INJURIES OF THE EYES

Introduction

6.1 Among the survivors of mustard gas attacks in World War 1 (1914-18) and the Iran-Iraq conflict (1980s) skin, eye and respiratory injuries were almost universal. Mortality is, however, low – 2% in World War 1 and 3-4% in the Iran-Iraq conflict.

6.2 Eye exposures occur in 80-90% of casualties. Reactions vary from mild conjunctivitis (75% of cases) to moderate and severe keratoconjunctivitis. It is this latter group with corneal involvement that requires ophthalmological attention may have severe and long-standing ocular sequelae.

6.3 Sulphur mustard exists as a straw coloured fluid, slightly soluble in water and is aerosolised when dispersed or spread by an explosive force. It is highly toxic and has low volatility so that it may persist for more than a week in closed spaces, open spaces with little wind and in temperate climates. Sulphur mustard rapidly penetrates the skin, but 80% will evaporate, and of the remainder 10% remains on the skin and 10% is absorbed systemically. Damage is from destruction of adhesion points between cells and basement membranes. It also binds to and alkylates DNA, enzymes, structural proteins and other macromolecules.

Literature review

6.4 A review carried out for this report identified the relevant literature to consider four aspects of management. Altogether, 1717 papers were identified of which 22 appeared relevant. The reference lists of these papers were also searched and these revealed another 16 papers of interest; these, in turn, allowed a further 6 papers to be found.

Results of review

- **Decontamination:** There are no observational human studies, controlled trials or even case reports concerning appropriate decontamination after mustard gas exposure but it is clear that the chemical is fixed in the cornea within 15 minutes.
- **Immediate general treatment:** There are no controlled trials concerning appropriate immediate general treatment of mustard gas exposure. Most recommendations are based on reading the historical literature and

* It is acknowledged that sulphur mustard is a volatile liquid at room temperatures and thus that the term “mustard gas” is not wholly appropriate. However, “mustard gas” is a widely used term and we have retained it in this account.

personal experience. Eyes exposed to mustard gas should be irrigated with copious amounts of water.

- **Specific treatment:** There are no reported observational human studies or controlled trials concerning appropriate immediate specific treatment after mustard gas exposure. What little evidence there is, is experimental and based on experiments in rabbits. Most recommendations are based on contemporary management of other types of chemical injury.
- **Pre-treatment:** There are no known proven safe and effective pretreatments against mustard agent exposure of the eyes.

Recommended management

6.5 Although no clear evidence base is available from controlled studies, the following staging and intervention may be used based on present knowledge and experience.

1. **Immediate:** there may be few initial symptoms.
2. **Early:** (1 to 8 hours.) Lid swelling and eye closure, grittiness, lacrimation, photophobia, blepharospasm and impaired vision.
3. **Intermediate:** (1 to 10 days.) Corneal epithelial loss, stromal opacification and thinning, secondary infection and uveitis.
4. **Late:** (Months-Years.) Abnormalities of limbal vascular bed with ischaemia and ulceration.

Treatment

6.6 The priority is to remove the casualty from the contaminated area. Contaminated clothing should be removed as soon as possible and the skin washed with soap and water, as mustard gas penetrates the skin within a few minutes.

Immediate. Speed of decontamination is extremely important and immediate irrigation is needed to minimise damage to the cornea. While isotonic fluids such as saline might have theoretical advantage they are rarely available in quantity at the point of contamination. The need for speed is such that the use of large quantities of clean water is therefore recommended. During irrigation, the eye is held open, ideally with the aid of topical anaesthetic drops. The lids should be held away from the globe. Copious fluid should be irrigated into the eye and allowed to drain for at least 30 minutes to leach out all possible traces of active chemical from the ocular tissue. Any particulate matter should be removed straight away. Patients with eyes exposed to mustard gas should be reassured, given systemic analgesics and dark glasses. Petroleum jelly can be used to prevent lid adhesion. Bandages should be avoided.

Early and Intermediate (0-10 days) Early assessment is vital to determine the extent and severity of the injuries. This should include the features listed in Table 6.1. The extent of the corneal chemical injury can be graded (Table 6.2). Admission to hospital is advised if there are grade 3 or 4 changes. Intraocular damage, especially if accompanied by a raised intraocular pressure indicates a poor prognosis. In the mild forms, grades 1-2, epithelial healing can occur in the first few days.

Table 6.1. Initial clinical assessment of chemical eye injury

Visual acuity	unaided and with pinhole
Pupil	reactivity and presence of afferent pupil defect
Lids	extent of burns, necrosis
Conjunctiva and Limbus	epithelial loss, necrosis, ischaemia, symblepharon formation
Cornea	epithelial loss, oedema, stromal opacity
Anterior chamber	fibrin, uveitis, lens debris.
Iris	atonicity, haemorrhage
Lens	opacity, leakage
Intraocular pressure	low, normal, raised

Table 6.2. Grading for severity of chemical burns

GRADE	PROGNOSIS	SIGNS	ISCHAEMIA
1	Good	Epithelial damage	none
2	Good	Cornea hazy Iris details visible	>1/3 limbus
3	Guarded	Total epithelial loss Stromal haze Iris details obscured	1/3—1/2 limbus
4	Poor	Cornea opaque Iris and pupil not visible	>1/2 limbus

Some or all of the following may be used by ophthalmologists. Ideally, preservative free topical drops should be used where available.

- 1. Steroids** – up to hourly for the first week and then gradually tapered off. In the early phase, the anti-inflammatory leucocytic inhibitory action of steroids is valuable to prevent secondary tissue damage by invading polymorphs. In the longer term, their use may impair epithelial regeneration and collagen repair, together with corneal melt. Therefore their use ought to be reduced after the first week.

- 2. Vitamin C or potassium ascorbate drops** – up to every hour. Vitamin C acts as a cofactor in collagen synthesis, and as an antioxidant, and may prevent damage by chemically active free radicals, released at the time of injury. Intraocular vitamin C is rapidly depleted in severe chemical burns and anterior segmented ischaemia prevents its transport into the eye. The use of topical vitamin C has been shown to be effective in experimental chemical burns. Use G Ascorbic 10%, or sodium citrate 10% (eye drops) hourly, and discontinue when the epithelium has healed.
- 3. Acetylcysteine** four times a day for up to two weeks. This donates sulfhydryl groups, which contribute to the cross linkage and maturation of new collagen and inhibits collagenase enzymes, which are released at the time of tissue damage.
- 4. Antibiotics.** If there is loss of corneal epithelium, their use prevents secondary infection. Chloramphenicol drops or Fluoroquinolones 4 times a day.
- 5. Pupil Dilation** with atropine 1% or cyclopentolate 1% drops twice daily, until the acute phase is over.
- 6. Corneal Protection** If there is significant damage to the lid or corneal exposure, in any form, remedial treatment is a moist protective chamber, constant lubrication with preservative free drops, such as Hypromellose or Celluvisc hourly or Lacri-Lube ointment 6 times a day.
- 7. Lids** Topical steroid and antibiotic treatment as required. Check that no symblepharon has formed, and rod or use a contact lens as required.
- 8. Analgesics.** Nerve endings will be damaged and pain may be severe. Adequate analgesics are required.

Late Management

6.7 Long -term treatment should be by a corneal specialist. The initial treatment is to allow the epithelium to heal. Further management may include removal of necrotic tissue, a bandage contact lens, a penetrating corneal graft, amniotic membrane graft, limbal cell transplantation for the cornea, and mucus membrane and amniotic membrane grafts for the lids. The techniques used will depend on the severity of the injury and are outside the role of these guidelines, which are for the acute treatment only.

Recommendation Regarding Monitoring of Efficacy of Treatment

6.8 We recommend that a particularly careful record should be kept of the outcome of treatment using the various methods listed above. Experience in this field is limited in the UK and the identification of approaches that are demonstrably valuable would be helpful.

Summary

6.9 This review was prepared with the aid of the Royal College of Ophthalmologists. The opportunity to consult a group of specialists in diseases of the cornea (the Bowman Group) was also taken.

6.10 All ocular injuries, which are likely to be bilateral and symmetrical, should be managed by vigorous and copious irrigation with water as soon as possible which can be aided by the use of topical anaesthetic drops. Although initially distressing the majority of ocular injuries from mustard gas make a full recovery.

6.11 Injuries that are persistent in signs or symptoms should be referred for specialist opinion.

6.12 Although there is no evidence base for specific ocular treatment, ophthalmologists are likely to use at their discretion; topical mydriatics, antibiotics, and steroids plus membrane removal and insertion of symblepharon rings (to separate the bulbar from the palpebral conjunctiva).

6.13 Other agents that *may* have a part to play in early management include; topical vitamin C, acetyl cysteine, and systemic nonsteroidal anti-inflammatory /analgesic agents.

6.14 Other treatments in the longer term for severe cases *may* include; therapeutic bandage, contact lenses, amniotic membrane transplantation and limbal stem-cell allografts.

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CHAPTER 7

RECOMMENDATIONS FOR RESEARCH

Introduction

7.1 Research into methods of counteracting the effects of the chemicals considered in this report has, in some cases, been underway since their use during the First World War. Rapid advances are perhaps unlikely and before discussing possible approaches the issues requiring operational research are discussed.

7.2 In cases of poisoning by nerve agents and hydrogen cyanide, treatments exist but have to be given as quickly as possible after poisoning to be effective. It is appreciated that in the setting of a terrorist incident there is likely to be a delay between exposure to a toxic substance and administration of therapy. Reducing this interval is very important. It is recommended that operational research is undertaken with a view to achieving this.

7.3 It is made clear in several sections of this report that assisted respiration and oxygen are mainstays of effective patient management. It is appreciated that providing such assistance in a mass casualty situation will be very difficult and that these difficulties may be added to by the need for decontamination of patients before admission to hospital. However, it is recommended that operational research designed to reduce the interval between exposure and access to this form of care be undertaken. Research into how best to provide assisted respiration and supplementary oxygen to as many patients as possible is also recommended.

Specific recommendations

(i) *Oxime therapy in nerve agent poisoning*

A systematic investigation should be undertaken of the $t_{1/2}$ of aging and reactivation of inhibited human erythrocytic acetylcholinesterase using the three oximes, P2S, obidoxime and HI-6. The nerve agents used should include tabun, sarin, soman, VX and cyclosarin. The study design should include a time course of reactivation, at various different concentrations of nerve agent and no means should be used to inhibit aging.

A systematic investigation should be undertaken of the antidotal efficacy of the three oximes, P2S, obidoxime and HI-6 in soman, cyclosarin and tabun poisoning. This would need to be carried out in primates, and could not usefully be done in any other animal.

Non cholinesterase-reactivating effects of bis-pyridinium compounds (obidoxime, HI-6, HLö-7 and bis-pyridinium non-oximes) should be further studied, especially in soman poisoning but also in tabun poisoning. (In the

latter reactivation with most oximes *in vitro* is slow and this raises the question of whether non-cholinesterase reactivating effects are responsible for the benefit sometimes observed *in vivo*).

The studies recommended should be carried out without pyridostigmine pre-treatment and should be continued for a clinically relevant time to model the circumstances that are likely to prevail in the event of a nerve agent exposure in a civilian population in the UK.

(ii) *Antidotes for cyanide poisoning*

Further work is recommended on the antidote hydroxocobalamin. This offers, in principle, a low toxicity alternative to the conventional antidotes: dicobalt edetate and sodium nitrite. Much work has been done on the use of hydrocobalamin in victims of smoke exposure where both hydrogen cyanide and carbon monoxide may play a part in any poisoning. Less is known about the efficacy of hydroxocobalamin in pure hydrogen cyanide poisoning. The need for rapid confirmation of cyanide poisoning prior to treatment is recognised and research into better means of detecting exposure to cyanide is recommended,

(iii) *Treatment for exposure to lung damaging agents*

Much work is underway on the pathophysiology and treatment of pulmonary oedema. This is especially so in the field of post traumatic pulmonary insufficiency or adult respiratory distress syndrome. Despite many years of work in this area no simple and effective means of reversing the process has appeared and treatment continues to depend largely upon supportive care with carefully controlled ventilation as needed. Free radical scavenging agents have been examined in some detail and it may be that recent advances in understanding of how free radicals damage cells will allow advances to be made. Before any specific recommendations for research can be made an in depth review of this area is needed: this is recommended.

GLOSSARY AND ABBREVIATIONS

Acetylcholine:	Neurotransmitter at neuromuscular junctions, at autonomic ganglia, in the central nervous system and at post-ganglionic parasympathetic nerve endings
Acetylcholinesterase:	Enzyme found in red blood cells, at neuromuscular junctions, parasympathetic effector sites, autonomic ganglia and in the central nervous system. Catalyses the breakdown of acetylcholine to acetic acid and choline
AChE:	Acetylcholinesterase
Aging	In the context of nerve agents, a process of monodealkylation of the nerve agent-acetylcholinesterase complex which renders the complex unreactivable, either spontaneously or by pyridinium oximes
Amyl nitrite	Methaemoglobin-generating cyanide antidote. Can be inhaled
Atropine:	Compound that blocks muscarinic acetylcholine receptors. Use produces dilation of the pupils and an increased heart rate. It is used in nerve agent poisoning to counteract the effects of increased amounts of acetylcholine that result from inhibition of acetylcholinesterase
Avizafone:	A soluble prodrug of diazepam that is compatible for IM injection with atropine and pralidoxime mesilate and is included in some autoinjection devices such as the L4A1 ComboPen
AVPU:	The AVPU scale allows rapid assessment of a casualty's state of consciousness. (<u>A</u> lert responds to <u>V</u> oice, responds to <u>P</u> ain, <u>U</u> nresponsive)
Cyclosarin:	A liquid nerve agent of moderate volatility (cyclohexyl methylphosphonofluoridate). GF.
Dexamethasone:	A synthetic steroid drug

Diazepam:	Widely used sedative compound of the benzodiazepine group of drugs.
Dicobalt edetate:	An EDTA chelate of cobalt ions. The commercial preparation contains free cobalt ions.
4-Dimethylaminophenol	A methaemoglobin-generating cyanide antidote
DMAP	4-Dimethylaminophenol
DOX:	Doxycycline: an antibiotic
EDTA:	Ethylenediamine tetra-acetic acid. Used as disodium EDTA, a chelating agent. This agent binds divalent metals such as calcium or cobalt.
ETYA:	5,8,11,14-eicosatetrayanoic acid. A substrate analogue used to reduce production of prostaglandins
Frusemide:	A diuretic drug
GA:	Tabun, ethyl <i>N</i> -dimethylphosphorocyanidate
GB:	Sarin, isopropyl methylphosphonofluoridate
GD:	Soman, pinacolyl methylphosphonofluoridate
GF:	Cyclosarin, cyclohexyl methylphosphonylfluoridate
GSH:	Glutathione. A natural antioxidant found in the body
HCN	Hydrogen cyanide
HI-6:	A pyridinium oxime (asoxime chloride)
Hydrogen cyanide	Liquid or gas that blocks electron transport and thereby oxidative metabolism
Hydroxocobalamin	Vitamin B12a, a cyanide antidote. It consists of cobalt at the centre of a corrin structure and a nucleotide

Methaemoglobin:	Haemoglobin contains iron in the divalent, reduced, ferrous state. Oxidation to the ferric (trivalent) form produces methaemoglobin. Methaemoglobin does not reversibly bind to oxygen but does bind to cyanide ions to form cyanmethaemoglobin
Mustard gas:	Dichlorodiethylene sulphide. Sulphur mustard. A vesicant widely used in World War I. A liquid at room temperature
NAC:	N-acetylcysteine: a synthetic antioxidant drug
Nerve agents:	Organophosphorus compounds of great toxicity, developed as chemical warfare agents
Obidoxime	A pyridinium oxime
Oximes:	Pyridinium oximes are compounds that increase the rate of dissociation of an organophosphorus compound from acetylcholinesterase. Pralidoxime mesilate, obidoxime and HI-6 are pyridinium oximes. Oximes comprise a very large group of compounds, with diverse properties but pyridinium oximes, in terms of the treatment of organophosphate compounds are frequently simply referred to as oximes.
Pralidoxime mesilate (P2S):	A pyridinium oxime
Prostaglandins:	Large series of physiologically active compounds derived from unsaturated long chain fatty acids. These compounds play a part in inflammatory reactions in the body/ Production is inhibited by the anti-inflammatory drug aspirin
Pyridinium oximes	These are compounds that increase the rate of dissociation of an organophosphorus compound from acetylcholinesterase.
Pyridostigmine:	A carbamate drug that reversibly inhibits acetylcholinesterase
RADS:	Reactive airways dysfunction syndrome. A syndrome produced by exposure to high concentrations of gases such as chlorine

and characterised by an enhanced bronchoconstrictor response to airway irritants.

Sarin:	A volatile liquid nerve agent, chemical name isopropyl methylphosphonofluoridate.
Sodium nitrite	Methemoglobin generating cyanide antidote
Sodium thiosulfate	Cyanide antidote that acts as a co-factor in the conversion of cyanide to the less toxic thiocyanate ion
Soman:	A liquid nerve agent of moderate volatility. Chemical name pinacolyl methylphosphonofluoridate.
Sulphur mustard	Mustard gas
Symblepheron:	Adhesions between the conjunctiva lining the eyelids (palpebral conjunctiva) and that covering the white of the eye (bulbar conjunctiva). Management includes gentle breaking down of adhesions by means of a glass rod or insertion of a ring to prevent adhesions forming.
Tabun:	Nerve agent produced in Germany in the late 1930's: liquid of moderate volatility. Chemical name: ethyl <i>N</i> -dimethylphosphorocyanidate
Uveitis:	Inflammation of the middle or uveal coat of the eye. The area comprises the iris, the ciliary body and the very vascular choroid that supports the retina
Vesicant	Substance that causes blistering of the skin.
VX:	This nerve agent has no common name. A liquid of low volatility with the chemical name <i>o</i> -ethyl- <i>s</i> -[2(diisopropylamino)ethyl] methylphosphonothioate.

ANNEX 1

General Management of Casualties contaminated by Chemical Compounds

This paper deals with the specific management of casualties poisoned by selected chemical compounds. Although the management of poisoning for individual chemical agents may be specific, the initial management is the same and has been summarised below:

Airway – the airway of the casualty must be maintained at all times. In the unconscious casualty this may involve simple basic airway manoeuvres plus suction of the copious secretions associated with chemical poisoning. Occasionally, there may be a requirement for advanced airway management, such as tracheal intubation, to protect the airway from the excessive secretions and to prevent aspiration of regurgitated stomach contents.

Breathing must be carefully observed until full decontamination and recovery have occurred. Supplemental oxygen will speed the recovery from volatile chemical poisoning. If breathing becomes compromised it must be supported by artificial ventilation with supplemental oxygen using a self-inflating resuscitation bag-valve-mask or automatic ventilator. Entrained air must be filtered when ventilating casualties in a contaminated environment.

Circulation must be carefully observed and monitored. Non-invasive blood pressure, pulse oximetry and ECG monitoring are all useful indicators of circulatory function. The early establishment of intravenous access will aid the administration of fluids and drugs.

Disability should be assessed using the simple AVPU scale (**A**lert, responds to **V**oice, responds to **P**ain, **U**nresponsive). This assessment should be repeated at frequent intervals to assess the progress of the casualty.

Drugs, especially the specific antidotes, should be administered as per the description in the text.

Exposure of the casualty is essential not only to assess physical damage but to remove all clothes that have been contaminated by the chemical.

Environment. It is important to remember that the primary management described above may be severely limited by the need of the rescuer to wear protective clothing. Therefore only those skilled in these techniques and trained in protective clothing should enter and treat casualties in a contaminated area. All others should await the casualties' arrival in cold/clean zone, following decontamination.

It should be remembered that the identification of the chemical and therefore its specific antidote might take some time. However this must not delay the basic medical management of the casualty.

ANNEX 2

Membership of the Expert Group on Management of Chemical Casualties Caused by Terrorist Activity (EGMCCT)

Chairman	Professor P G Blain CBE	
Members	Dr D Baker Mr C Green Professor K Mackway-Jones Dr T C Marrs Dr V Murray Dr P Rice Mr G Roberts Dr D Russell Dr J Simpson Dr J Thompson Dr J A Vale Dr D Zideman	
Secretariat	Dr R L Maynard CBE Miss J P Cumberlidge	(DH) (DH)
Observers:	Mrs Judith Field Dr I Giarchi	(DH) (DH)