

# Toxicology and Military Anaesthesia

TC Nicholson-Roberts

Specialist Registrar Anaesthesia and Intensive Care Medicine, MDHU Derriford

## Abstract

**The combination of trauma and poisoning is a situation likely to be faced by a deployed force at some point. This article provides practical advice on how to deal with poisoned patients without deviating from the concept of damage control resuscitation. The constraints of limited diagnostics, both at the scene and clinically, and lack of antidotal therapy are fundamental to the practice of clinical toxicology. Some of the specific therapies such as atropine and oximes were not evaluated prior to their introduction and there are few randomised controlled trials of poisoned patients. Most of the diagnoses will be made on clinical grounds and most of the therapy will be supportive; this article aims to reassure military anaesthetists in the process of dealing with the poisoned trauma patient.**

## Introduction

The changing landscape of toxicological threats to deployed troops might now be inclined towards toxic industrial chemicals (TICs). Exposure to these can be classified as an accidental or deliberate release and the casualties may or may not have associated trauma. For example, in the Bhopal disaster of 1984, an accidental release of methyl isocyanate, resulted in no direct trauma but thousands of poisoned patients. The Buncefield Oil Storage Depot fire in 2005 had the potential to cause serious injury including blast and burns with the associated effects of inhaled combustion products and particles. Deliberate release would include the Iraq chlorine tanker incidents in 2007 [1]. Fortunately the temperature of the blasts were such that a large proportion of the chlorine burnt and that which did not, was dissipated, however the accompanying blast would have resulted in much trauma. In the management of a suspected chemical release, the identification of the compound, its combustion and reaction products are advantageous. Whilst this is relatively straightforward in the UK from registration of COMAH (Control of Major Accident Hazards) sites, the use of HazChem and a myriad of other data sources, it will be extremely difficult on operations. This knowledge is important, not only to determine scene management but also to establish levels of exposure and the effects arising from that. The importance of physicochemical properties such as solubility, volatility and reactivity are not confined to scene management. They are of equal importance in considering a compound's journey through release, absorption, distribution to and metabolism by internal organs. These properties will not be known until much later during the management of a release and toxicological data will follow from that. From the innumerable TICs only a small fraction have antidotes or specific therapies that need instituting, most require supportive therapy only, and will be considered later.

Predicting likely chemical scenarios is always difficult and different agencies will come up with various solutions. In general terms threats were first described in quasi-mathematical form by J David Singer over 50 years ago: *Threat perception = Estimated Capability x Estimated Intent* [2]. Whilst few traditional chemical warfare agents were discovered in Iraq, other threats such as

chlorine abound. Rumours of chemical attacks on schools by Taliban indicate a degree of intent [3], however the exact nature of the agents used is not in the public domain. Locals likened the odour to that of a compound used to poison foraging birds [4]. Although the intent is high, the capability so far is limited to toxic substances readily available until superior agents become available to those hostile elements.

The very nature of poisoning dictates that well performed studies are difficult, much data is derived from animal models, case reports and the experience of a few individuals. The poisoned patient presenting for surgery introduces an extra dimension to the care required. The immediate need for damage control resuscitation may result in continued treatment of poisoning in the operating theatre. Those patients who may be disadvantaged by general anaesthesia, for example in organophosphate poisoning, should have a regional anaesthetic technique where possible to avoid clouding of clinical assessment.

## Burns and Toxic Industrial Chemicals

There are many thousands of chemicals in everyday use; some are inherently poisonous or react with others to become so, or form toxic products of combustion. Trauma in the presence of burns should be managed according to established guidelines with attention to management of airway burn, aggressive fluid resuscitation and prevention of sepsis. Early intubation is mandatory in the presence of an inhalation injury. After a burn extrajunctional expression of acetylcholine receptors is increased, there is a general agreement that after a delay of 24h or more then suxamethonium-induced hyperkalaemia becomes a real risk [5]. Potassium ions will leak out of myocytes in greater amounts, as a greater number of receptor ion channels are then held open by suxamethonium. On the other hand, non-depolarising neuromuscular blocking agents (NMBAs) require a dose increase. Inhalation injuries represent a huge spectrum of illness dependent on duration of exposure, concentration, composition and temperature of smoke. A simple house fire will result in production of significant quantities of carbon monoxide (CO) and hydrogen cyanide (HCN). The abundance of synthetic materials, some containing halogens and nitrogen, contribute to HCN formation and also to inorganic acids and nitrogen oxides with lung damaging properties [6]. Virtually all TICs have no specific treatment and supportive therapy with appropriate organ support, good nursing care and attention to microbial sampling is all that can be offered.

**Corresponding Author: Major TC Nicholson-Roberts BSc MRCP(UK) FRCA DipMedTox RAMC, Specialist Registrar Anaesthesia and Intensive Care Medicine, MDHU Derriford, Brest Road, Plymouth PL6 5YE**  
Email: [tcnr@doctors.org.uk](mailto:tcnr@doctors.org.uk)

### Smoke Inhalation

Although rare, inhalation injury makes a considerable contribution to mortality and morbidity from burns. Efficient heat exchange in the upper airway reduces the risk of lower airway thermal injury, but will not protect from soot, inorganic acids and other toxins. Hypoxaemia results from shunt; blockage of bronchi by secretions, diffusion impairment; capillary leak and loss of hypoxic pulmonary vasoconstriction mediated by reactive oxygen and nitrogen species [7]. Cell necrosis will inevitably result in cytokine release and a generalised inflammatory response [8]. Lung compliance may be reduced by more than 50% in the first 24h due to surfactant loss and increases in extravascular lung water and pulmonary lymph flow [9].

The presence of hypoxia, pulmonary oedema or bronchospasm aside from anticipated or actual airway problems are indications for tracheal intubation and a period of postoperative ventilation and supportive care. This must include bronchial hygiene therapy and physiotherapy to effect the removal of retained secretions and casts [9], as the mucociliary escalator will have been destroyed or disabled. Fraction of inspired oxygen ( $F_i O_2$ ) and positive end expiratory pressure (PEEP) are titrated against arterial oxygen tension ( $P_a O_2$ ) and peripheral oxygen saturation ( $SpO_2$ ); a protective ventilatory strategy is adopted for acute lung injury. There have been no well controlled studies comparing different modes of ventilation in inhalation injury [9]. Other supportive measures are outside the scope of this article but must include adequate nutrition and attention to microbiological sampling and tissue viability. There is limited evidence to suggest that nebulised heparin and N-acetylcysteine can improve outcome in severe inhalation injury [9,10]. These measures are unlikely to cause harm in themselves provided bronchodilators are used to counter the possibility of N-acetylcysteine mediated bronchospasm. Other simple measures include bronchoscopy to confirm inhalation injury and bronchial lavage with 1.4% sodium bicarbonate [11].

### Carbon Monoxide

Carbon monoxide poisoning (CMP) should be assumed, and if possible excluded, in any patient exposed to smoke, particularly in a confined space. It is a product of incomplete combustion of hydrocarbons and other carbon containing substances - in isolation it is colourless and odourless. Features of CMP include headache, nausea and cerebral irritation (Table 1). Loss of consciousness from cerebral oedema, myocardial ischaemia and acidosis occur in severe poisoning. It is possible that personnel accommodated in an environment with significant carbon monoxide from incomplete combustion by a heater could all present with symptoms mimicking 'flu or food poisoning. Thus CMP should be considered when faced with an outbreak of food poisoning or 'flu-like symptoms. It will not be filtered by conventional personal protective equipment (PPE). The pathophysiology of CMP is complex, based upon extreme left shift of the oxyhaemoglobin and myoglobin dissociation curves and interfering with the mitochondrial respiratory chain and cellular oxygen utilisation. Common problems include cardiovascular injury, to heart and vascular endothelium and neurological injury, particularly to 'watershed areas' of the brain such as basal ganglia, with some long term sequelae [12,13]. Most blood gas analysers will measure carboxyhaemoglobin automatically, non-smokers will have a level <5% and smokers may be up to 10%. This measured level has no prognostic significance and should not be used to guide therapy as

the half life of carboxyhaemoglobin is variable and does not reflect binding to cytochromes; it merely confirms the diagnosis.

Oxygen saturation as measured by oximetry will be high, however oxygen carried by carboxyhaemoglobin is effectively unavailable due to left shift of the oxyhaemoglobin dissociation curve. Carboxyhaemoglobin has a half life of 4-5h under normal conditions, falling to 40-80min if the patient is breathing 100% oxygen. The half life of carbon monoxide bound to cytochromes is likely to be longer. [13-15]

| %COHb | Expected Symptoms and Signs                                                 |
|-------|-----------------------------------------------------------------------------|
| <10   | Usually Nil                                                                 |
| 11-20 | Headache, exertional dyspnoea, cutaneous blood vessel dilation              |
| 21-30 | Throbbing headache, weakness, dizziness                                     |
| 31-40 | Severe headache, nausea, vomiting, confusion, dizziness, weakness, collapse |
| >40   | Increasing CNS effects with respiratory failure                             |

**Table 1. Anticipated effects of initial carboxyhaemoglobin (COHb) level [13].**

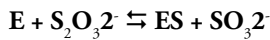
Thus the added considerations for supportive care to the carbon monoxide poisoned patient presenting for surgery is to increase the fraction of inspired oxygen and take precautions against raised intracranial pressure; head up tilt, maintain normotension, normocapnoea and normothermia, care with tracheal tube ties and regular assessment of pupils. There is little data on duration of oxygen therapy; logic would dictate that therapy continues until the patient is better. However it might be reasonable to continue for five carboxyhaemoglobin half lives or three and a half hours in the case of patients in need of post-operative ventilation. The lack of availability, in the operational environment, and inconclusive evidence of hyperbaric oxygen therapy precludes further discussion here.

### Cyanides

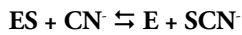
Cyanide production results from fires involving burning of plastics with high nitrogen content, examples include polyurethane and acrylics. In these situations carbon monoxide poisoning is highly likely to coexist which has diagnostic and treatment implications. Cyanide poisoning is difficult to diagnose; information from the history provides the best marker of exposure. Signs and symptoms are vague, such as headache, dizziness, tachycardia and tachypnoea [5,13]. Cyanide acts at a mitochondrial level by poisoning the electron transport chain, forcing anaerobic metabolism. Assays exist but only in a handful of hospitals and certainly not on deployed operations; the diagnosis should be assumed with a consistent history and significant carboxyhaemoglobinaemia. Tissue oxygen uptake is severely impaired, leading to a high central venous oxygen saturation ( $S_{cv} O_2$ ) and a rise in lactic acid from forced anaerobic metabolism. It seems logical that a high  $S_{cv} O_2$  or an unresolving hyperlactataemia are indications for cyanide antidote therapy. This is backed up by a study in carbon monoxide poisoned dogs which demonstrated a rapid recovery in haemodynamic and metabolic variables, except lactataemia, on cessation of cyanide infusion [16].

Hydrogen cyanide is a naturally occurring chemical and a mechanism for its elimination has evolved. It is when this mechanism is overwhelmed that toxicity occurs, this is due to

a relative deficiency of sulphur donors. Sodium thiosulphate ( $\text{Na}_2\text{S}_2\text{O}_3$ ) given intravenously acts as a sulphur donor for the enzyme rhodanase (thiosulphate: cyanide sulphurtransferase) located in mitochondria. This is a slower process than chelation by dicobalt edetate. First the rhodanase enzyme ( $E$ ) forms a persulphide link with the thiosulphate ion [17]:



Rhodanase is then cycled back to the sulphur free form [17]:



By doing so, cyanide ( $\text{CN}^-$ ) is converted to relatively harmless thiocyanate ( $\text{SCN}^-$ ) which is excreted by the kidney. In the unlikely event that the diagnosis is confirmed then dicobalt edetate 300mg in 50ml of 50% glucose can be given [13,18,19]. Dicobalt edetate chelates cyanide in order that the kidneys can excrete it. There is a risk of hypotension, arrhythmias, laryngeal and facial oedema if dicobalt edetate is given in the absence of cyanide poisoning [19]. In reality the diagnosis will *not* have been confirmed and a safer approach is to use sodium thiosulphate 12.5g over 10min [19]. Formation of methaemoglobin using amyl nitrate or sodium nitrite is a strategy that has been used in severe cyanide poisoning. Cyanide avidly binds methaemoglobin reducing the amount binding to cytochromes, the bound cyanide is metabolised by the mechanisms outlined. Of course this will reduce the oxygen carrying capacity of blood which may be compromised already by a significant proportion of carboxyhaemoglobin. Inducing methaemoglobinaemia in a patient with carboxyhaemoglobinaemia is not recommended unless there has been a significant cyanide exposure with mild carboxyhaemoglobinaemia.

Accordingly, trauma anaesthesia for the cyanide poisoned patient must involve an index of suspicion in cases of smoke inhalation where there is hyperlactataemia contributing to a raised anion gap acidosis and a high central venous oxygen saturation. Sodium thiosulphate is likely to be the safest antidote unless cyanide poisoning is confirmed; other complications such as fits are managed in a conventional fashion.

### Chlorine

Chlorine is in widespread use in industry and is familiar to all of us. Chlorine was used with devastating effect during the First World War [20], nowadays it is involved in both accidental (Figure 1) and deliberate releases.



Chlorine is a largely predictable toxin. The effects of chlorine are predominantly in the eyes and respiratory tract and are worse with increasing dose, duration of exposure and in cases with underlying lung disease. Early features are, predictably, a sore throat, cough, chest tightness and dyspnoea [22]. Laryngeal oedema, bronchospasm and pulmonary oedema are seen with increasing doses (Table 2).

| Concentration |                           | Effect                                         |
|---------------|---------------------------|------------------------------------------------|
| 1-3ppm        | 3-10mgm <sup>-3</sup>     | Mild mucous membrane irritation after 60min    |
| 5-15ppm       | 15-45 mgm <sup>-3</sup>   | Moderate irritation of upper respiratory tract |
| 30ppm         | 90 mgm <sup>-3</sup>      | Immediate chest pain, vomiting, coughing       |
| 40-60ppm      | 115-175 mgm <sup>-3</sup> | Pneumonitis and pulmonary oedema               |
| 430ppm        | 1250 mgm <sup>-3</sup>    | Lethal after 30min                             |
| 1000ppm       | 2900 mgm <sup>-3</sup>    | Fatal within a few minutes                     |

**Table 2. Anticipated effects of increasing concentrations of chlorine [23].**

Cases of chlorine poisoning are managed in a supportive fashion as acute severe asthma with bronchodilator therapy and nebulised steroids, however the role of corticosteroids is not completely established [21]. In more severe cases, pulmonary oedema is managed in conventional fashion with non-invasive continuous positive airway pressure (CPAP) and tracheal intubation if that fails.  $\text{F}_1\text{O}_2$  and PEEP are titrated against  $\text{P}_a\text{O}_2$  and  $\text{SpO}_2$  and a protective ventilatory strategy adopted for acute lung injury. Chlorine toxicity can be delayed such that a period of post operative observation should include the anticipation of respiratory problems in patients with asymptomatic exposure.

### Phosgene

Phosgene is widely used in the chemical manufacturing industry, however in UK most use is in factories that manufacture phosgene on site. This has virtually eliminated the transport of phosgene on the road and rail networks. It was first used as a War Gas during World War 1; initial exposure resulted in few symptoms and was succeeded by florid pulmonary oedema, sometimes up to a day later [20].

**Figure 1. Chlorine release from a tanker in the 2005 Graniteville, South Carolina rail crash. Approximately 54 tonnes (35 000 litres) of chlorine escaped from a ruptured tanker resulting in 8 deaths: according to the Coroner's verdicts, seven were from asphyxia and one, the Train Engineer, who died several hours post-exposure from 'lactic acidosis'. 554 casualties attended local hospitals with breathing difficulties, 75 of those were admitted [21]. Note that Chlorine does not always take on the textbook yellow-green colour; it can also appear brown. It is denser than air and, in the absence of wind will settle in low areas.**

Photo: Environmental Protection Agency

In common with other lung damaging chemicals there is no specific therapy for phosgene inhalation [24]. Lung damage occurs as a result of free radical generation leading to lipid peroxidation and associated glutathione depletion [24]. Supplementation or repletion of glutathione may be of value as demonstrated by a study in isolated rabbit lungs [25]. Postoperative patients exposed to phosgene require minimal exertion for 48h with close observations to identify the development of pulmonary oedema. The use of steroids remain controversial and are probably not indicated. At present supportive therapy using a protective ventilatory strategy with nebulised N-acetyl cysteine and bronchodilators is indicated; pulmonary oedema is managed with PEEP.

## Chemical Weapons

The NATO definition of chemical weapons states that they are substances intended for use on military operations to kill, injure or incapacitate as a result of their physiological effects. This does not confine their use to the battlefield as seen in Tokyo 1995 when sarin was released in the underground. Cyanides, chlorine and phosgene have all been weaponised and the management of the poisoned soldier during conflict does not differ in these circumstances.

## Lung Damaging Agents

Lung damaging agents, also known as choking agents include chlorine, phosgene and hydrochloric acid. These are non-persistent agents that do not require decontamination in current theatres of operations. Treatment is supportive and if patients survive the first 48 hours they usually recover without sequelae [26].

## Blister Agents

Vesicants or Blister Agents were first used during World War I to cause burning and blistering of exposed areas. They include the mustards and lewisite. They are persistent in temperate and colder climates. Unless they have been 'thickened', decontamination should not be required in hotter climates, however vapour concentrations can be higher under these circumstances. The effects of mustards are due to oxidation and alkylation of DNA, RNA and other important biological molecules. Crosslinking of DNA and RNA at guanine residues results in cytotoxicity, errors in DNA repair mechanisms can result in transformation and malignancy. Decontamination of kit and equipment is beyond the scope of this article, however the surgical patient with blister agent exposure may require ongoing decontamination in the operating theatre. Contaminated clothing fragments should be placed in a bleach solution to prevent further vapour release, wounds are irrigated with 3000- 5000ppm chlorine (dilute Milton) solution before rinsing with crystalloid [27]. Mustards are degraded by water, forming hydrochloric acid. During its manufacture 0.9% Saline is rendered acidic with hydrochloric acid and therefore may not be the ideal solution to irrigate with. Decontamination of eyes and mucous membranes should not be attempted using skin decontamination preparations but 1.26% (isotonic) sodium bicarbonate should be used to irrigate if available, otherwise saline or Hartmann's solution will have to substitute. Mydriatics should be used in corneal damage to prevent adhesions with the iris and local anaesthetics should be avoided, permanent blindness is rare [27]. For intraperitoneal, intrathoracic and intracranial wounds crystalloid is used as irrigation fluid.

Lung manifestations occur after a latent period up to six hours beginning with symptoms of a severe upper respiratory tract infection. Burning throat pain results in a reluctance to cough until copious secretions supervene. Epithelial necrotic fragments and

pulmonary oedema will lead to hypoxaemia from shunt, diffusion impairment and a predisposition to pneumonia exacerbated by immune dysfunction [27]. There is a strong correlation between conjunctival damage and lung injury [27]. Lung support is achieved in a conventional fashion with escalation as necessary from non-invasive to invasive ventilation with titration of PEEP and  $F_{I}O_2$  against  $P_aO_2$ .

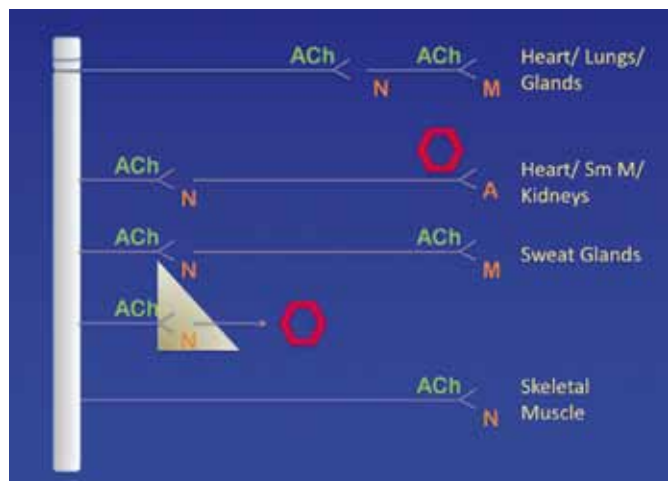
Skin damage occurs within two minutes of exposure and progresses through erythema, blistering to full thickness burns. Skin damage is worst in warm wet skin [27]. The blister fluid is not vesicant and generally the blisters are not painful in postoperative patients with adequate systemic analgesia.

Lewisite is an arsenical vesicant with a specific antidote, dimercaprol (British Anti Lewisite) which is used in metalloid and heavy metal poisoning. The onset of symptoms is faster than with mustard and although lung effects are less severe, blindness is more likely. Dimercaprol ointment can be applied to decontaminated skin and eyes or injected intramuscularly in severe exposure [27]. Perioperative management is as for mustard.

## Organophosphorus compounds

Organophosphorus (OP) compounds include the nerve agents and agricultural insecticides; other infrequent uses are as fire retardants and lubricants. The commonest cause of organophosphorus morbidity is from accidental or intentional ingestion from the agricultural sector.

OPs are irreversible inhibitors of plasma, red cell and tissue esterases, particularly butyrylcholinesterase (BChE) and acetylcholinesterase (AChE). It is inhibition of AChE that gives rise to the classic features of the cholinergic phase of nerve agent toxicity. This is brought about by overwhelming cholinergic stimulation by acetylcholine in the central nervous system, neuromuscular junction and autonomic nervous system. A summary of the effect sites of acetylcholine is shown in Figure 2.



**Figure 2.** An outline of the utilisation of acetylcholine by the autonomic nervous system and neuromuscular junction. The parasympathetic effects are demonstrated at the top where pre and post ganglionic fibres are stimulated by acetylcholine (ACh) at nicotinic (N) and muscarinic (M) receptors. Preganglionic sympathetic fibres are generally shorter than those in the parasympathetic nervous system, nevertheless they utilise ACh to stimulate nicotinic receptors. The postganglionic sympathetic fibres release catecholamines shown as red hexagons acting viscerally, and hormonally from the adrenal gland demonstrated by the brown triangle. Crucially the sympathetic innervation of sweat glands is by ACh acting on muscarinic receptors.

The characteristics of OP toxicity are outlined in Table 3. Cholinergic crises are not only seen in indirectly acting toxins such as OPs and carbamates, such as pyridostigmine, but also with directly acting cholinomimetics, fungi and betel, sodium channel openers, some animal venoms and aconitine poisoning.

| Central Nervous System.<br>Nicotinic and Muscarinic Effects | Autonomic Nervous System                             |                                                 | Neuromuscular Junction.<br>Nicotinic Effects |
|-------------------------------------------------------------|------------------------------------------------------|-------------------------------------------------|----------------------------------------------|
|                                                             | Parasympathetic Nervous System<br>Muscarinic Effects | Sympathetic Nervous System<br>Nicotinic Effects |                                              |
| Confusion                                                   | Bradycardia, Hypotension                             | Tachycardia, Hypertension                       | Muscle weakness                              |
| Agitation                                                   | Bronchospasm, Bronchorrhoea                          | Sweating                                        | Paralysis                                    |
| Coma                                                        | Salivation, Vomiting, Diarrhoea                      | Mydriasis                                       | Respiratory failure                          |
| Respiratory Failure                                         | Miosis, Lacrymation, Urination                       |                                                 | Fasciculation                                |

**Table 3. Summary of effects of OP poisoning. Generally the parasympathetic features prevail to the extent that mydriasis is not seen and hypovolaemia must be excluded as a cause of tachycardia should it occur. Note the multiple causes of respiratory failure and how all except the neuromuscular junction's contribution can be reversed by atropine. After Eddleston et al [28].**

Low dose exposure to OPs may mimic an outbreak of influenza or gastroenteritis. On deployed operations the diagnosis is clinical. There may be no history (Figure 3); casualties presenting with pin point pupils, profound salivation, respiratory distress and bradycardia should least arouse suspicion of OP poisoning and fasciculations are almost pathognomic. Assays for BChE and red cell AChE will not be available in the field. They are classed as specialist or infrequent assays ideally available within three hours including journey time in UK [29]. BChE activity more closely tracks the clinical picture [28, 29] except in patients with suxamethonium apnoea.



**Figure 3. Mother and child who have succumbed to nerve agent as a result of the attack on Halabja 16 March 1988. Observe the dried copious secretions from lacrimation and salivation. It is thought that mustard and cyanide were also used [30]**

Photo: Sipa Press/ Rex Features Ltd with permission

OPs bound to AChE become less likely to dissociate through a process known as ageing. Ageing is thought to represent loss of an alkyl group which means that the complex is less likely to undergo spontaneous dephosphorylation. Of the nerve agents, ageing occurs most rapidly with soman with a  $t_{1/2}$  (time required for half the enzyme to become resistant to reactivation) of 1.3 minutes, whereas the ageing  $t_{1/2}$  of sarin is five hours and that of tabun, 46 hours [31]. Recovery is by synthesis of new enzyme which occurs at a rate of about 1% per day [32].

Morbidity and mortality is primarily due to hypoxia from bronchospasm, bronchorrhoea and failure of ventilation by central and peripheral mechanisms. After the initial cholinergic phase follows a period of delayed neuromuscular weakness and respiratory failure first described as the Intermediate Syndrome [33], however further observations have demonstrated less of a distinction and a variable constellation of signs [34]. The Intermediate Syndrome has not been observed in cases of nerve agent poisoning [35] and there is no mention of it in the NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B) [36]. It is not clear why this is and clinicians should at least be alert to the possibility of it occurring.

The principles of therapy include pre-exposure prophylaxis, maintenance of oxygenation during acute exposure and maintaining a period of post exposure observation in cases of agricultural OP poisoning. Pre-exposure prophylaxis is usually achieved using pyridostigmine 30mg eight hourly. Carbamates bind AChE less avidly, however they disrupt the binding of OPs to the extent that reactivation of AChE is made easier. Unbound OPs undergo hydrolysis before spontaneous dissociation of the carbamylated AChE produces active enzyme. Pyridostigmine should be discontinued once nerve agent poisoning has occurred as any unaffected AChE will be required to function. Unaffected patients who have been taking pyridostigmine may require antimuscarinic premedication and are likely to require increased doses of non-depolarizing neuromuscular blockers intraoperatively.

The patient with OP poisoning presenting for surgery will need resuscitating first, and in patients who have been issued them, combopens may have been used. They contain atropine 2mg, pralidoxime 500mg and avizafone which is a diazepam prodrug, equivalent to 5mg. The overarching principle is maintenance of oxygenation and this is chiefly achieved by atropine in conjunction with standard resuscitative measures. In the presence of hypoxia or where oxygen supplementation is unavailable there is always the concern of precipitating ventricular tachyarrhythmias, however this is not borne out by clinical practice in agricultural OP poisoning [28]. Atropine will rapidly decrease bronchospasm and dry secretions, thus alleviating hypoxia. A useful guide to atropine dosing is shown in Figure 4 which illustrates doubling of doses as recommended by Eddleston [28]; rapid atropinisation is crucial in severe OP poisoning and should take precedence over giving other drugs. One should give as much as it takes to reach a heart rate greater than 80 beats per minute and to break

the bronchospasm, either by assessing lung compliance through positive pressure ventilation, including bag valve mask, or by auscultation in the self ventilating patient. Assessment of pupils should not guide atropine dosing. An infusion of atropine after 'loading' may result in a smoother recovery profile [28,36].

An oxime such as pralidoxime is given as soon as practicable in order to restore some AChE activity, however it is ineffective in the aged OP-AChE complex. There is evidence that it will bind unbound OPs, preventing their binding to AChE [32]. Oxime infusions have been used after the loading dose - pralidoxime should be started at 2.1 mgkg<sup>-1</sup>h<sup>-1</sup> [36].

Fitting is commoner in nerve agent than agricultural OPs and should be treated in conventional fashion using diazepam. Agitated patients should also receive diazepam provided atropine is being given; paradoxically respiration under these circumstances is enhanced [37].

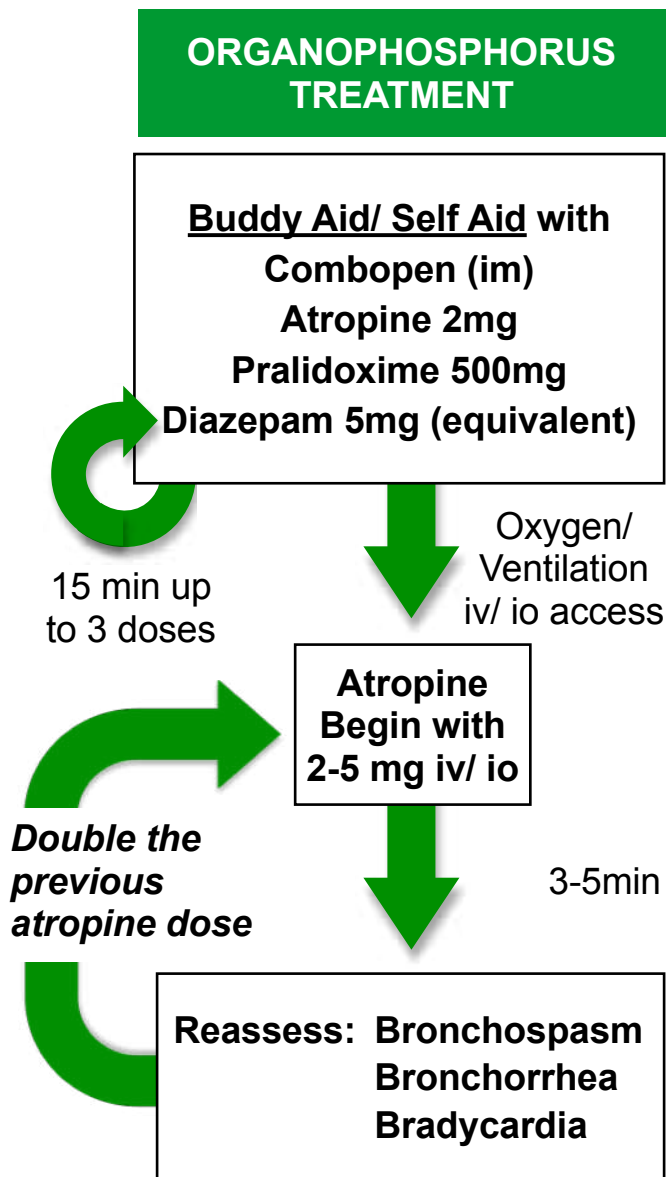
During the acute cholinergic phase, muscle relaxation will not be necessary as in moderate to severe poisoning the patient will already be paralysed and suxamethonium action will be greatly prolonged. Similarly, after carbamate pre-exposure prophylaxis the carbamylated BChE will not hydrolyse suxamethonium as readily resulting in prolonged action. It may be the case that non depolarising neuromuscular blockers will shield post synaptic nicotinic receptors from excess ACh stimulation during the acute phase [35]. Whether this is beneficial is not known. A type II neuromuscular block is one that exhibits fade on repeated stimulation and potentiation after induced tetany. It is usually seen after the administration of non-depolarising neuromuscular blockers and in the Intermediate Syndrome. It can be assessed using a conventional theatre monitor; the 'train of four' [32]. Consequently relaxants should be used with great care or avoided altogether in the Intermediate Syndrome. There is very little clinical experience in this regard.

Other measures can be employed to hasten recovery such as decreasing ACh at the synaptic cleft. Drugs such as magnesium and clonidine reduce ACh secretion in central and peripheral neurones. Magnesium will also be useful in averting torsade de pointes in the event of severe poisoning sufficient to prolong the QT interval. Currently, there is little evidence to support the use of magnesium. A small study in Tehran of agricultural OP poisoning demonstrated a reduction in mortality and length of stay in an unrandomised and unblinded trial [38]. A larger Sri Lankan study is ongoing and will provide further clarification [39].

Surgery for the OP poisoned patient should be embarked upon following restoration of oxygenation and further therapy can be given intraoperatively. Consideration should be given to regional anaesthesia and interpretation of monitoring will be confused by a heart rate driven by atropine. It is likely, however in the event of OP poisoned patient(s) arriving at a Field Hospital that they will encounter anaesthetic expertise in managing a condition that is not too far removed from their own clinical experience.

### Future Developments

OP poisoning represents a serious threat to health with approximately 200 000 deaths per year [28,32] mainly in developing countries. Advances in research by organisations such as the South Asian Clinical Toxicology Research Collaboration are limited by funding. Advances made in the military sector are often kept secret. Scavenging of OPs before they have bound AChE is an area that is currently under investigation, this can only be accomplished with rapid intervention and may reduce length



- Establish 2nd iv access and give Pralidoxime 2g over 5-10 min and infusion at 2.1 mgkg<sup>-1</sup>h<sup>-1</sup> if dermal or gastric absorption continues
- Diazemuls 5mg every 5min iv if fitting
- Continue atropine until HR >80 and bronchospasm is broken
- Consider fluid replacement of losses
- Consider atropine infusion of 10-20% of "loading dose" per hour

Figure 4. An algorithm for the treatment of OP poisoning, combopen use is currently unlikely. Atropine is given in doubling doses until atropinisation is achieved, an infusion of 10-20% of that total dose can then be given per hour. Benzodiazepines should be given routinely in nerve agent poisoning but are less likely to be required in agricultural OP poisoning. Cutaneous VX absorption will continue after decontamination and will necessitate infusions of pralidoxime and atropine. After Bland [40] and Eddleston et al [28].

of stay. Recombinant BChE has been trialled *in vitro* and binds OPs stoichiometrically [41]. Another avenue that may be worth pursuing is the use of cyclodextrins. They have been in use for many years in pharmaceutical preparations but have only recently been

used as drugs in the form of sugammadex that stoichiometrically binds the neuromuscular blocking agents rocuronium and vecuronium [42,43]. Sequestering of OPs by cyclodextrins is a possibility and candidates could rapidly be screened for activity as the act of sequestering represents a reduction in entropy. Any useful prototypes would therefore cool the reaction vessel. Whilst sequestering is useful, cyclodextrins can be modified to become catalysts [44] and this has been investigated with resulting hydrolysis of soman by  $\beta$ -cyclodextrins [45,46]. Unfortunately, due to rapid aging of soman this may not be clinically useful.

Another possible spin off from the world of anaesthesia is the use of intralipid for local anaesthetic toxicity. So far there are two theories as to its mechanism of action; the lipid sink hypothesis and modulating carnitine acylcarnitine transferase activity in cardiac mitochondria [47,48]. A lipid sink hypothesis may provide another method of scavenging and there is a current vogue for using intralipid successfully in various scenarios of massive drug overdose refractory to conventional resuscitative methods [49,50]. Whether this might work in OP poisoning remains to be seen.

## Conclusions

Military anaesthetists are familiar with the requirement for damage control resuscitation in military trauma [51]. Poisoned trauma patients will, at some point be delivered to a field hospital and undue delays in resuscitation will be detrimental. The additional complication of poisoning in trauma patients should not represent undue difficulty for the military anaesthetist in guiding the trauma patient through the perioperative period. There are few antidotes as compared to the number of potential toxins out there; most treatment is supportive and reacting to changes in physiology.

## References

- Russell D. Personal communication. 13 March 2009
- Singer JD. Threat-Perception and the Armament-Tension Dilemma. *J Confl Resolut* 1958; **2**: 90-105
- Stratfor Global Intelligence. Afghanistan: Schools Targeted by Chemical Weapons. May 12, 2009 [http://www.stratfor.com/analysis/20090512\\_afghanistan\\_schools\\_targeted\\_chemical\\_weapons](http://www.stratfor.com/analysis/20090512_afghanistan_schools_targeted_chemical_weapons) accessed 13 July 2009.
- The New Zealand Herald. Afghanistan: Young girls targeted in 'Taleban gas attack'. May 13 2009 [http://www.nzherald.co.nz/world/news/article.cfm?c\\_id=2&objectid=10572008](http://www.nzherald.co.nz/world/news/article.cfm?c_id=2&objectid=10572008) accessed 13 July 2009.
- MacLennan N, Heimbach D, Cullen B. Anesthesia for Major Thermal Injury. *Anesthesiology* 1998; **89**: 749-770
- Alarie Y. Toxicity of Fire Smoke. *Crit Rev Tox* 2002; **32**: 259-289
- Traber DL, Hawkins HK, Enkhbaatar P *et al.* The role of the bronchial circulation in the acute lung injury resulting from burn and smoke inhalation. *Pulm Pharmacol Therapeut* 2007; **20**: 163-166
- Nguyen TT, Gilpin DA, Meyer NA, Herndon DN. Current Treatment of Severely Burned Patients. *Ann Surg* 1996; **223**: 14-25
- Mlcak RP, Suman OE, Herndon DN. Respiratory management of inhalation injury. *Burns* 2007; **33**: 2-13
- Miller AC, Rivero A, Ziad S, Smith DJ, Elamin EM. Influence of nebulized unfractionated heparin and N-acetylcysteine in acute lung injury after smoke inhalation injury. *J Burn Care Res* 2009; **30**: 249-56
- Oxford Desk Reference: Critical Care. Waldman C, Soni N, Rhodes A. Oxford University Press. 2008. Chapter 28.7 Burns-general management
- Hardy KR, Thom SR. Pathophysiology and treatment of carbon monoxide poisoning. *J Toxicol Clin Toxicol* 1994; **32**: 613-29
- Maynard R, Thompson J. Personal communication 13 February 2008
- Calman K, Moores Y. Carbon Monoxide: The Forgotten Killer. Department of Health CMO Letter. 7 September 1998
- Henry JA. Carbon monoxide: not gone, not to be forgotten. *J Accid Emerg Med* 1999; **16**: 91-103
- Breen PH, Isserles SA, Westley J, Roizen MF, Taitelman UZ. Combined carbon monoxide and cyanide poisoning: A place for treatment? *Anesth Analg* 1995; **80**: 671-7
- Gliubich F, Gazerro M, Zanotti G, Delbonoi S, Bombieri G, Bernii R. Active Site Structural Features for Chemically Modified Forms of Rhodanese. *J. Biol. Chem.* 1996; **271**: 21054-21061
- Bland SA. Personal communication. 12 July 2009
- British National Formulary Number 57. March 2009.
- Harris R, Paxman J. A Higher Form of Killing. Random House Publishing USA Inc 2002
- Collision of Norfolk Southern Freight Train 192 With Standing Norfolk Southern Local Train P22 With Subsequent Hazardous Materials Release at Graniteville, South Carolina January 6, 2005. Railroad Accident Report. NTSB/RAR-05/04. PB2005-916304. Notation 7710A Adopted November 29, 2005. National Transportation Safety Board, 490 L'Enfant Plaza SW, Washington DC 20594
- Agabiti N, Ancona C, Forastiere F *et al.* Short term respiratory effects of acute exposure to chlorine due to a swimming pool accident. *Occup Environ Med* 2001; **58**: 399-404
- International Programme on Chemical Safety (IPCS) (1996). Chlorine. Poisons Information Monograph. PIM 947
- Russell D, Blain PG, Rice P. Clinical management of casualties exposed to lung damaging agents: a critical review. *Emerg Med J* 2006; **23**: 421-424
- Sciuto AM, Holcombe HH. Therapeutic Treatments of Phosgene-Induced Lung Injury. *Inhal Tox* 2004; **16**: 565-580
- NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B) Part III – Chemical. 1 February 1996. Chapter 4: Lung Damaging Agents (Choking Agents)
- NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B) Part III – Chemical. 1 February 1996. Chapter 3: Vesicants (Blister Agents)
- Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. *Lancet* 2008; **371**: 597-607
- National Poisons Information Service and Association of Clinical Biochemists. Laboratory analyses for poisoned patients: joint position paper. *Ann Clin Biochem* 2002; **39**: 328-339
- BBC: On This Day. 16 March 1988. Accessed 24 August 2009. [http://news.bbc.co.uk/onthisday/hi/dates/stories/march/16/newsid\\_4304000/4304853.stm](http://news.bbc.co.uk/onthisday/hi/dates/stories/march/16/newsid_4304000/4304853.stm)
- United States Environmental Protection Agency. Office of Pollution Prevention and Toxics. NERVE AGENTS GA, GB, GD, GF (CAS Reg. Nos. 77-81-6, 107-44-8, 96-64-0, and 329-99-7) October 2000
- Karalliedde L. Organophosphorus poisoning and anaesthesia. *Anaesthesia* 1999; **54**: 1073-1088

33. Senanayake N, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Eng J Med* 1987; **316**: 761-763
34. Eddleston M, Mohamed F, Davies J *et al.* Respiratory failure in acute organophosphorus pesticide self-poisoning. *Q J Med* 2006; **99**: 513-522
35. Anesthesia and Perioperative Care of the Combat Casualty. Specialty Editors Brigadier General Russ Zajtchuk, Christopher M Grande. Published by the Office of The Surgeon General at TMM Publications 1995. Borden Institute, Walter Reed Army Medical Center, Washington, DC 20307-5001. Chapter 30: Anesthesia for Casualties of Chemical Warfare Agents. Baker DJ, Rustick JM
36. NATO Handbook on the Medical Aspects of NBC Defensive Operations AMedP-6(B) Part III – Chemical. 1 February 1996. Chapter 2: Nerve Agents
37. Dickson E, Bird S, Gaspari R, Boyer E, Ferris C. Diazepam inhibits organophosphate-induced central respiratory depression. *Acad Emerg Med* 2003; **10**: 1303-06
38. Pajoumand A, Shadnia S, Rezaie A, Abdi M, Abdollahi M. Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides. *Hum Exp Toxicol* 2004; **23**: 565-569
39. South Asian Clinical Toxicology Research Collaboration. [http://www.sactrc.org/hospital\\_current\\_research\\_activities.html](http://www.sactrc.org/hospital_current_research_activities.html) accessed 1 September 2009
40. Bland SA. Personal communication. 12 July 2009
41. Huang Y-J, Huang Y, Baldassarre H *et al.* Recombinant human butyrylcholinesterase from milk of transgenic animals to protect against organophosphate poisoning. *Proc Natl Acad Sci* 2007; **104**: 13603-13608
42. British National Formulary 57 March 2009 15.1.6 Drugs for reversal of neuromuscular blockade > Other drugs for reversal of neuromuscular blockade
43. Naguib M. Sugammadex: Another Milestone in Clinical Neuromuscular Pharmacology. *Anesth Analg* 2007; **104**: 575-581
44. Easton C. Cyclodextrin-based catalysts and molecular reactors. *Pure Appl Chem* 2005; **77**: 1865-1871
45. Desire B, Saint-Andre S. Interaction of Soman with b-Cyclodextrin. *Tox Sci* 1986; **7**: 646-657
46. Seltzman H, Lonikar M. Catalytic beta-cyclodextrin enzyme mimics as soman hydrolases. *Proceedings of the Medical Defense Bioscience Review* 1993; **3**: 1075-1083
47. Weinberg G, Palmer J, VadeBoncouer T, Zuechner M, Edelman G, Hoppel C. Bupivacaine inhibits acylcarnitine exchange in cardiac mitochondria. *Anesthesiology* 2000; **92**: 523-8
48. Picard J. Lipid emulsion to treat overdose of local anaesthetic: the gift of the glob. *Anaesthesia* 2006; **61**: 107-109
49. Young A, Velez L, Kleinschmidt K. Intravenous fat emulsion therapy for intentional sustained-release verapamil overdose. *Resuscitation* 2009; **80**: 591-593
50. Finn S, Uncles D, Willers J, Sable N. Early treatment of a quetiapine and sertraline overdose with Intralipid. *Anaesthesia* 2009; **64**: 191-194
51. Jansen J, Thomas R, Loudon M, Brooks A. Damage control resuscitation for patients with major trauma. *Brit Med J* 2009; **338**: 1436-1440