Pathophysiological aspects of clinical management following toxic trauma

D. J. Baker

Introduction
Exposure to toxic agents may occur as a result of accidental or deliberate release. Accidental release of industrial chemicals may produce small scale incidents or mass disasters such as that which occurred in Bhopal in 1984. Deliberate release occurs when toxic agents are deliberately used as weapons of war or by terrorists. The consequences for medical management systems, of both accidental and deliberate release are considerable. This article considers the clinical presentation of a selection of the most common toxic agents from a pathophysiological standpoint.

Toxic trauma
The term ‘toxic trauma’ was coined by the International Trauma Anesthesia and Critical Care Society in 1996 to describe the injury caused by the mass release of toxic agents. Conventional physical trauma implies tissue damage from external forces causing a chain of events leading to cellular and organ failure. Toxic trauma causes direct cellular damage and tissue hypoxia leading to cell and organ failure. Blunt trauma also causes direct cellular damage while penetrating trauma causes cell death via hypovolaemia, underperfusion and tissue hypoxia (Box 1).

Systemic attack by toxic agents
Box 2 shows body systems which may be affected by toxic agents. Some systems such as the nervous and respiratory systems may be affected rapidly to produce life-threatening respiratory failure. Such is the case with pesticide and nerve agent poisoning. Other systems such as the epithelial and other cellular systems may be affected with a longer latency to produce blistering and burning. This is the case with mustard gas exposure. Internal effects of this agent may produce blistering and

Box 1: Trauma—a unified concept

- Physical trauma
  - Penetrating
  - Blunt
- Shock, hypovolaemia, failure of oxygen transfer and mitochondrial processes – lysosome release and cell death
- Toxic trauma
  - Multisystem attack
- Direct and indirect failure of oxygen transfer and mitochondrial processes – lysosome release and cell death
- Mixed trauma
  - Explosive or combusting release of toxic agents causing multiple trauma (physical and toxic)

Box 2: Specific toxic agent attack on somatic systems

1. agents affecting the epithelial system
   - Vesicants (eg mustard gas)
   - Ricin
2. agents affecting the respiratory system
   - Upper, lower airway
     - Lung damaging agents (eg phosgene, isocyanates)
   - Respiratory control system
     - Organophosphates
   - Gaseous exchange
     - Pulmonary oedemagens
   - Mechanics of respiration
     - Organophosphates
     - Toxins (eg botulinum toxin)
   - Cellular respiration
     - Cyanide
3. agents affecting the central nervous system
   - Organophosphates
   - Cyanide
   - Neuropeptides
   - Agents of anaesthetic origin (eg phencyclidines, BZ)
4. agents affecting the peripheral nervous system
   - Neuropeptides
   - Neurotoxins (botulinum, saxitoxin)
5. agents affecting the immune system
   - Mustard gas
   - Ricin
6. agents affecting the heart and circulatory systems
   - Organophosphates
7. agents affecting the alimentary and renal systems
   - Organophosphates
   - Toxins
desquamation in the airways leading to airway blockage.

The respiratory system is the most immediately vulnerable to toxic attack both in terms of structure and function. The end results on the airways are blockage, increased resistance and decreased compliance. Effects on the breathing control system lead to failure of lung ventilation. Actions on the muscles of the thoracic cage have the same effect. The production of toxic pulmonary oedema causes a diffusion failure in oxygen passage leading to hypoxaemia.

**Organophosphate attack on the cholinergic nervous system**

Organophosphate (OP) and carbamate compounds affect the central and peripheral cholinergic nervous systems through inhibition of acetyl cholinesterase (AChE).\(^1\) Examples of such compounds are sarin and insecticides such as fenthion. Inhibition of AChE causes increased concentrations of acetyl choline at muscarinic and nicotinic sites. The signs and symptoms relate to the basic pharmacology of the cholinergic nervous system and include actions on the parasympathetic system such as bradycardia and myosis, excess salivation, vomiting and diarrhoea and involuntary micturition. Effects on the voluntary nervous system include muscle fasciculation and an initial depolarizing flaccid paralysis. OP also attack central GABA receptors causing spike discharges and convulsions. There is also a syndrome of re-paralysis with a non–depolarizing block (Intermediate Syndrome—see below). Finally there is long term neural attack though neurotoxic esterase inhibition.

Atropine, often in high dosage is used to block the muscarinic actions of OP but the alkaloid has no specific action at the voluntary nicotinic synapses. Therapy here depends upon the use of oximes to regenerate the cholinesterase. Compounds used include pralidoxime, obidoxime or the newer Hagedorn oximes such as HI 6.\(^5\)

Life-threatening convulsions may be controlled by diazepam. A combination of pralidoxime, atropine and lysine-diazepam is the basis of the military immediate use injection following nerve agent exposure. Airway clearance and artificial ventilation are a vital part of the management of OP exposure. The development of small gas powered ventilators powered by compressed oxygen has allowed early provision of IPPV of a quality usually associated with hospital care in the pre-hospital area. Ventilatory support is now part of many major toxic response plans.\(^6\)

Apart from the acute cholinergic syndrome the OP Intermediate Syndrome (IMS) presents a pathophysiological development following OP exposure which has important consequences for subsequent clinical management. Sennanayake and Karralliede in 1987\(^7\) described a re-paralysis of 10–20% of patients at 18–24 hours post OP pesticide exposure following resolution of the acute cholinergic syndrome. There was an apparent change in the nature of NM block with indications of decrementing responses, signifying a non–depolarizing block. IMS affects proximal limb, cranial motor and respiratory muscles. The syndrome was confirmed by many authors during the 1990's with neurophysiological evidence pointing to post–neuromuscular junctional lesion.\(^8\) Clinical analogies exist for the syndrome including dual block following prolonged succinyl choline, first described when this anaesthetic technique was used during the 1950s and 60s.\(^9\) There are also similarities with myasthenia gravis where there is an immune based down–regulation (reduction in density of AChR at the post–junctional membrane).

Clinical neurophysiological studies of IMS\(^5\) have indicated fade at low frequency stimulation and absence of post-tetanic facilitation which point to a post-junctional lesion. More information may be provided from single fibre electromyography (SFEMG), a sensitive neurophysiological technique which records action potentials from two muscle fibres innervated by a common terminal pathway.\(^10\) Analysis of the time variations between the potentials (jitter analysis) gives information about the safety margin of AChR at the NMJ. In conditions where this is reduced such as myasthenia gravis, Eaton Lambert syndrome and administration of non–depolarising muscle blockers such as curare the jitter increases and in some cases leads to a failure of firing of muscle fibres, known as blocking. Significant degrees of blocking are detected as fade following conventional repetitive stimulation but SFEMG will detect changes in neuromuscular transmission long before they are evident using conventional techniques and clinical observation. Baker and Sedgwick\(^11\) reported an SFEMG study of eight fit volunteers exposed to trace amount of sarin (corrected
RBC AChE inhibition 40%). The study showed small increased jitter changes seen at three hours post exposure with overall increased jitter changes seen at three days post exposure. No clinical neuromuscular deficit was apparent. Jitter profiles were normal between one and two years post exposure. These results may indicate a sub-clinical change in NM safety margin after non-toxic OP exposure.

A number of possibilities have been advanced to explain the origins of the Intermediate Syndrome. These include neuropathy and myopathy together with pathophysiology of the neuromuscular junction itself. Neurophysiological evidence suggests that the NMJ is the critical site and debate centres around whether pre- or post-junctional receptors are involved. At the present time consideration of analogous clinical conditions suggests that it is down regulation of the AChR which is responsible but evidence remains lacking.

The third stage of clinical presentation of OP intoxication is organophosphate–induced delayed neuropathy. This is thought to be an action of the OP on the neurotoxic esterase enzyme system and is not related to the anticholinesterase properties of the compound.

Botulinum toxin
This toxin, produced by the anaerobe Clostridium Botulinum, has the reputation of being the most toxic substance by weight known to man, being at least 5000 times more toxic than sarin. Botulism is a disease of both man and animals. Seven different functionally–related neurotoxins are produced by various strains (A–G). Botulism is essentially an intoxication, brought on by ingestion of the toxin produced by clostridial infection of food, usually incorrectly canned meats. Primary botulism, a direct infection, is rare and only affects infants in the human species. The interest of botulinum toxin as a toxic agent is that it can be relatively easily produced by fermentation processes (which have been developed to produce antitoxins) and is stable in an aerosol, making mass delivery a theoretical possibility. Botulinum intoxication can however be treated and this modifies the toxicity considerably. It is estimated that less than 10% of natural cases receiving ventilatory and antitoxin support are fatal.

Botulinum toxin acts at the nerve terminal of cholinergic synapses and blocks the release of acetyl choline. After being taken up into the vesicles and translocated to the cytoplasm where the toxin catalyses proteolysis of components involved in the calcium–mediated exocytosis of ACh. The inhibition is permanent and recovery occurs only after the creation of new terminal boutons. The toxin thus blocks neurotransmission, parasympathetic synapses and peripheral ganglia. Conventionally after ingestion of the toxin (the usual route) the parasympathetic action produces a dry mouth, followed by signs of a progressive bulbar palsy (dysarthria, dysphasia and dysphagia) and ocular signs (diplopia and ptosis). Following this there is a progressive symmetrical descending muscular weakness leading to respiratory failure requiring prolonged ventilatory support. NM testing shows a classical presynaptic decremental pattern to repeated stimuli with post–tetanic facilitation. Single fibre electromyography will detect the neuromuscular changes before conventional nerve stimulation; there is increased jitter and blocking which is reduced by increasing the nerve firing rate. The pattern of signs and symptoms following a deliberate mass inhalation release is not known but botulinum toxin must be considered along with the nerve agents in any cases presenting with sudden cholinergic features.

Pulmonary oedemagens
Chemical–induced pulmonary oedema is a pathophysiological mechanism common to a wide range of compounds used both as chemical industrial intermediates and as military weapons. Toxic oedema may be defined as pulmonary oedema (PE) occurring after inhalation of toxic gases or vapours. It is a condition which develops with a variable latent period following exposure and is marked by acute and dramatic collapse of the patient. Toxic PE has produced the most dramatic mass casualties seen from the release of chemical substances. During the First World War phosgene was used by both sides and caused over 85% of all gas fatalities.

Box 3: Military and civil toxic oedemagens
Military chlorine-1915
phosgene-1915
PFIB
Civil (industrial intermediates, classified by HAZMAT)
phosgene
isocyanates
Bhopal, India (1984)
Phosgene exposure: a model for toxic pulmonary oedema

Phosgene is unique among chemical agents in that it has been used as a chemical warfare gas and also has major industrial applications at the present time. Phosgene is a liquid/vapour which can be formed accidentally by decomposition of chlorinated hydrocarbons. It has a major use as an intermediary in industrial syntheses. Both acute and chronic exposure to phosgene causes toxic PE. Exposure causes instant upper respiratory tract irritation but there is a latent period of 4–24 hours before the onset of toxic PE. This period is dose dependent: high dose: 1-4 hours; low doses 8-24 hours17 (see box 4).

Phosgene attacks primarily attack the lower airways and alveoli as a result of limited water solubility. There is a primary covalent attack on NH2 and SH substrates with free radical releases. Potential cell targets are type I and II pneumocytes and alveolar macrophages. Platelet aggregation in capillaries also occurs. Later there is a second line of attack with the release of prostaglandins causing vasoconstriction, vasodilation and bradykinin causing increased capillary permeability. In addition release of 5 HT causes constriction of postcapillary vessels. Thromboxane A2 leads to vasoconstriction and complement activating enzymes cause leucotriene release.18

The use of corticosteroids in toxic PE

There has been considerable debate about the rationale for the use of systemic and inhaled steroids in the treatment of toxic pulmonary oedema.

Theoretically there should be many advantages such as the inhibition of phospholipase A2 via induced lipomodulin and macrocortin. Inhibition of macrophages, inhibition of production of prostanoids and leucotrienes and stimulation of surfactant production in type II cells. However Diller18 felt the case for use to be unproven. Beneficial effects only follow early administration while late administration may be deleterious (inhibition of production of type I cells and enhanced fibroblast production). More recently studies have been published on animal models. Demnati et al19 showed a reduction in airway resistance following the administration of dexamethasone to chlorine exposed. Gunarsson and Walther20 published results from a pig study where inhaled beclomethasone showed improved PaO2, improved V/Q and less histological damage. However species differences exist and results should be applied with caution to man. At the present time use of inhaled steroids for developing toxic PE in man should not be discounted given the limited therapeutic options. Another tool to combat the development of toxic PE is the use of acetyl cysteine. The rationale is to increase intracellular glutathione levels to prevent lipid peroxidation induced PE. It is known that phosgene reacts with–SH groups and reduces GSH levels. Sciuto et al21 have published a study in which phosgene–exposed rabbits receiving n–acetyl cysteine treatment produced lower pulmonary wet weights and higher GSH levels inhibiting production of inflammatory leucotrienes.

Ventilation and developing toxic PE

The timing and technique of IPPV may have important consequences for the management of development of toxic PE. In particular the early use of bag valve mask ventilation may have deleterious effect on damaged alveolar tissue. It is known that automatic ventilation from portable emergency ventilators provides more accurate ventilation in the field than BVM techniques. Poorly controlled emergency ventilation may cause alveolar wall damage. It is now known that inappropriate ventilation in the intensive care unit may provoke ARDS due to kinin release due to repeated opening and closing of alveoli. This has lead to the ‘open lung’ strategy of pressure support ventilation where collapsed alveoli are opened and then kept open by application of PEEP and low tidal volumes.22,23 This technique may have an application in the early management of patients who are at risk of developing toxic pulmonary oedema.

Hydrogen cyanide

Hydrogen cyanide is one of several agents known formally as ‘blood’ agents although the term is a misnomer since the agent acts at the mitochondrial level of the cells. HCN in high concentrations is rapidly fatal. The LC50 has been estimated at 200 mg m⁻³ for 10 minutes.
HCN acts by binding to the iron atom in cytochrome oxidase enzymes inhibiting the catalytic function that allows oxygen to act as an electron receptor and thus produce ATP. This means that 'hypoxia' occurs at the tissue level which cannot theoretically be reversed by restoring oxygenation of the blood by resuscitation measures.

In the body HCN is broken down by rhodanase which detoxifies cyanide to thiocyanate. This process can be accelerated by provision of sodium thiosulfate which provides a store of sulfane sulfur for the enzyme. The usual dose of sodium thiosulfate is 50 ml of 25% solution. (pediatric dose 1.65ml/kg of 50% solution) It is usually administered in conjunction with sodium nitrite (300 mg given iv over 10 minutes (pediatric dose 0.15–0.33 ml/kg of 3 % solution) which causes the formation of methaemoglobin. This acts as a scavenger for HCN reducing plasma levels. Sympathomimetic support may be required for hypotension produced by sodium nitrite. HCN also reacts with heavy metals and this is the basis of the use of dicobalt edetate and hydroxycobalamin as cobalt providers for this reaction. Cobalt ions themselves are toxic but the toxicity can be countered by giving glucose which is part of standard therapy. Dicobalt edetate is thought to be more effective in the binding of cyanide ions that methemoglobin despite its secondary effects of hypertension and nausea.

It has long been believed that oxygen therapy and ventilation has no role in the treatement of cyanide intoxication since the blood is fully oxygenated in this condition. This view has however recently been challenged since some studies have shown that oxygen enhances the antidotal effects of the classical cyanide antidotes.

**Toxic agents causing direct cellular disruption (vesicants and toxins)**

Vesicant agents were first used as chemical weapons during the First World War. The most well–known is sulphur mustard (commonly known as ‘mustard gas’) It was used as a disabling agent but has a relatively long latency. Its successor Lewisite is an arsenic–based compound (2–chloro vinyl dichloarsine) is more volatile and has a short latency and causes immediate eye pain in addition to its vesicant properties. Mustard agent is the most commonly encountered vesicant. The reader is referred to standard reviews for the overall management of mustard gas injury which is the domain equally of the surgeon and specialised pulmonary physicians. ICU management presents longer term respiratory and metabolic problems. Eye and skin injuries fall within the aegis of other specialities.

Sulphur mustard (bis–2–chloroethyl sulphide) is a colorless or pale yellow oily liquid which indeed smells faintly of mustard. Its odour threshold is 1.3 mg /m3 which is below the concentrations usually reached in a battle–field and thus several minutes of detection are possible before incapacitating doses are reached. The LC50 is about 1500mg /min/m3 and the LC50 between 200 and 1000 mg/min/m3. Although the latency of action in cooler climates is about 4 hours information from the Iran–Iraq War, the scene of its most recent use, indicates that at higher ambient temperatures the agent has a far shorter latency and causes significant respiratory damage apart from its classical action as a skin vesicant.

Following exposure to mustard gas there is a latent period of between 4–12 hours following which there are ocular symptoms comprising eye pain, blurred vision and lachrymation accompanied by a diffuse erythema of exposed skin with oedema and first degree burns. The groin and genital area are particularly susceptible. Exposure to high doses produces severe cutaneous injury with necrosis. The burns bear some resemblance to thermal burns but are very slow to heal and are prone to secondary infection. The bullae characteristic of exposure to mustard agent are filled with a fluid that is not itself corrosive. A feature of exposure is that fluid–filled bullae appear for several days afterwards in an apparently random way (i.e. not cropped).

The respiratory effects of mustard exposure are important, particularly at high ambient temperatures. Following exposure there is an early tracheobronchitis with dry cough and hoarseness Heavy exposure will produce severe damage to the tracheal and main bronchial architecture with necrosis, sloughing and blockage A

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**Box 5: Cyanide exposure: Management**

- Removal from exposure: no decontamination required
- Accentuate natural rhodonase detoxification using thiosulphate as substrate (detoxification of cyanide to thiocyanate) (50 ml 25% solution)
- Sodium nitrite (300 mg over 10 minutes) to provoke formation of methaemoglobinaemia (scavanger for HCN)
- Dicobalt edetate and hydroxycobalamin as cobalt providers for reaction with CN
chemical bronchiolitis occurs at lower doses in high ambient temperatures and causes severe bronchospasm, requiring ventilation and intensive care. Lung damage following mustard exposure can be severe and permanent with chronic obstructive airways disease, bronchiectasis and reactive airways dysfunction syndrome.

Mustard agent acts at a cellular level forming highly reactive sulfonium ions which attack DNA by alklylation of sulfhydryl and amino groups. This causes the epithelial manifestations of exposure and also long term carcinogenesis, particularly of the skin, pharynx and respiratory tract. There is no specific treatment of mustard agent exposure but experimental studies in animals have shown a combination of sodium thiosulfate vitamin E and dexamethasone can improve survival and reduce organ damage. Willems has reviewed information concerning the clinical management of mustard gas casualties. The need for a proactive approach to airway management and ventilation is evident and intubation should be done early to allow adequate ventilation and access for debridement of the large airways. Willems reported that 87% of patients requiring ventilation died and thus the onset of severe respiratory symptoms is a serious development. Another point of concern for management is the leukopenia that follows exposure to mustard gas. This becomes evident 3–5 days after exposure and usually reaches its lowest point 7–9 days after exposure. Cellular replacement either peripherally or as marrow could be considered here since mustard is bound very quickly in the body following exposure and will not cause destruction of new cells.

Ricin

Ricin has been considered seriously as a terrorist threat since it can be extracted relatively easily from the seeds of the castor bean plant, Ricinis Communis. Waste from the production of castor oil contains about 5% ricin. Ricin has been used in assassination by injection and high inhaled concentrations are thought to be fatal. There is a substantial latent period before generalized signs and symptoms of the inhibition of protein synthesis occur including fever, abdominal pain, diarrhoea, drowsiness, confusion convulsions coma, weakness, cardiovascular collapse and respiratory failure, all progressing towards multiple organ failure and death within 36–72 hours. Treatment is supportive but an antitoxin has been developed for use in animals.

Conclusions

- Trauma following toxic exposure follows a number of defined pathophysiological processes
- Understanding of these allows a rational approach to the early and continuing management of casualties
- Direct cellular damage may occur but many toxic hazards act through a final common pathway of tissue hypoxia
- Early life support measures with rational antidote therapy can alter the clinical outcome

References