Chemical Warfare Agents:
Toxicity, Emergency Response and
Medical Countermeasures

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Topic 1. Chemical weapon toxicity and mechanisms of action

(a) Toxicity of nerve agents
(b) Toxicity of vesicants
(c) Long-term health effects of nerve agents and vesicants
(d) Human toxicological values of chemical warfare agent
Toxicity of nerve agents

Their main mechanism of toxicity is inhibition of AChE, the enzyme that degrades the neurotransmitter acetylcholine (ACh) at different sites of the body.

Inhibition leads to an accumulation of ACh in the synaptic cleft (neuromuscular junction) and prolonged stimulation of muscarinic and nicotinic receptors. This stimulation triggers various signs and symptoms such as widespread hypersecretions, bronchoconstriction, miosis, cardiovascular changes and convulsive seizures.

Respiratory effects can arise from a combination of peripheral changes (e.g. bronchoconstriction and airway over-secretion, diaphragm paralysis) or central effects (alteration of the respiratory drive) and can lead to death.
Toxicity of nerve agents

The toxicity mechanism depends on the route of exposure and toxicokinetics of the agent.

NAs (like sarin, tabun) can be dispersed in the form of liquid aerosols or vapours that will penetrate unprotected respiratory tract or mucosa.

Inhalation is the fastest way into blood and tissue distribution.

Low volatility, persistent NAs, like VX, can readily penetrate the skin. This route of poisoning is particularly difficult to treat because it results in a slower onset of poisoning and an extended exposure to the toxic agent.
Countermeasures of NA poisoning

- should be treated as a continuum: there is a need to recognise appropriate measures across the timelines of exposure and treatment.

- Controlling contamination is critical in casualty care.
Acute toxicity mechanisms of vesicants

Vesicants

- Sulfur Mustard
- Nitrogen mustards
- Lewisite
- Phosgene oxime

The massive inflammatory reaction that characterises poisoning by vesicants in general, and SM in particular, is followed by destruction of the affected tissue and further inflammation during the healing process.

There is a continuing need to identify early biochemical events to better understand the mechanisms that lead to vesicant injury. In this regard OMICS technologies and in vitro assay formats have shown great promise.
Organs usually affected after SM exposure

- Respiratory system
- Reproductive system
- Nervous system
- Skin
- Eye
- Blood
- Gastrointestinal
- Immune system
Long-term health effect of nerve agents and vesicants

Late complications:

- **respiratory tract** (78%) - dispnea, hemoptysis, pulmonary fibrosis, lung carcinoma, pneumonia, bronchial and tracheal stenosis, ephysema, chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, etc.
- **nervous system** (45%) – PTSD, chronic depression, loss of libido, anxiety...
- **skin** (41%) – dry skin, burning sensation, pruritus, atrophy, hypo- and hyperpigmentation, scarring...
- **eyes** (36%) - burning sensation, itching, blurred vision, vision loss, retina ulcer, corneal thining and opacity, keratitis, uveitis, conjunctivitis...

**Reproductive system** - Inhibition of spermatogenesis, sexual disfunction...

**Genotoxicity** - sister chromatid exchanges in the peripheral lymphocytes, varieties in enzymes involved in epigenetic changes

**Carcinogenicity** - lungs, larynx
Topic 2. Medical countermeasures and decontamination against chemical warfare agents

(a) Existing and future countermeasures against nerve agents and vesicants

(b) Current and emerging strategies for organophosphate decontamination
Existing and future countermeasures against nerve agents and vesicants

✓ Response time for treatment is critical and should be characterised and understood for the choice of countermeasures. AChE activity monitoring can be of critical importance to recognise exposure, before signs and symptoms of poisoning intensify.

✓ Oximes are not universally effective against AChE inhibited by different CWAs – more work is required to identify the most suitable oximes.

✓ Dosage must also be optimised for specific oximes due to the possibility of undesired side effects if they are administered in high dose.

✓ Countermeasures for lewisite (BAL and DMPS) chelate and remove arsenic from the site of injury, reducing the vesicant effect. More hydrophilic chelating agents are preferable to prevent BBB.

✓ There are many manuals on how to respond to chemical incidents, but there is little standardisation or response procedures for a general civilian population. A compilation of information categorised by whom it applies best to, could usefully serve as a reference collection.
Current and emerging strategies for CWs decontamination

- Validated and emerging strategies for CW decontamination include chemical, physical, and biological methods, with special attention to the use of decontaminating enzymes.

- Decontamination of people, equipment and the environment involves many types of materials and material properties. Best practices for use of decontamination solutions in contact with different surfaces and materials are important to understand.

Efficient toward G&V nerve agents
- no oral toxicity
- no dermal toxicity
- no environmental impact
Outcomes

a) Developments across the fields should be regularly monitored and efforts made to bring experts working in both civilian and governmental organisations together to share best practices.

b) New approaches to address old and continuing problems must also be considered. For example, sulfur mustard was first used as a weapon of war almost 100 years ago, yet to this day the precise mechanism by which it produces blisters is not understood. Only when it is, will it be possible to rationally design drugs that could be used to reduce or prevent blistering.

c) Treatment of exposure to toxic chemicals requires medical countermeasures and decontamination procedures (for victims of exposure, infrastructure and the environment).

d) On-site and point-of-care detection methods to identify exposure and trigger response to chemical agent exposure represent a first line of defence. Given the time-critical nature of treatment, a thorough review and evaluation of existing tools would be valuable for verification and investigative purposes.

e) There are many overlapping methods and technical dimensions in response to chemical agents and biological toxins, an example of the convergence of chemistry and biology. Efforts should be made to build networks that bridge communities of medical and emergency responders to share best practices and experience. These networks could be used to help maintain strong links between the SAB and the BTWC community.
Thank you for your attention!