What the новичок (Novichok)?
Why Chemical Warfare Agents Are More Relevant Than Ever

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#ITLS2018
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- **Dr. Sztajnkrycer is on the Editorial Board of International Trauma Life Support.**
Chemical weapons are becoming the new normal again, a century after World War I

The international community is sending a dangerous message: Stamping out chemical warfare is not a priority.

by Hamish de Bretton-Gordon / Nov.18.2017 / 3:31 AM ET

Sarin nerve gas WAS used in Assad's horrific attack on his own people that killed more than 90 people, international chemical weapons watchdog confirms

- WARNING: GRAPHIC CONTENT
- Organization for the Prohibition of Chemical Weapons carried out investigation
- It concluded Sarin gas was used in April 4 attack on the town of Khan Sheikhun
- United Nations-OPCW to now decide whether Syrian government was behind it
- Western intelligence agencies have blamed Assad's government for the attack
- But Syrian officials have repeatedly denied using banned toxins in the conflict

The 'taboo' against the use of chemical weapons may be fading, says Britain's military chief

Sir Stuart Peach says Canada and its allies need to keep chemical warfare from becoming the new normal

Murray Brewster - CBC News - Posted: Apr 06, 2018 3:45 PM ET | Last Updated: April 6
Specific CW Agents
Classes of Chemical Agents: The Big 5
The “A” List

- Pulmonary Agents
  - Phosgene Oxime, Chlorine
- Vesicants
  - Mustard, Phosgene
- Blood Agents
  - CN
- Nerve Agents
  - G, V, Novel, T
- Incapacitating Agents
Thinking Outside the Box - An Abbreviated List

- Ammonia
- Chlorine
- Phosphine
- Dibotane
- Allyl Alcohol
- TDI
- Nitric Acid
- Hydrazine
- Nitrogen Dioxide
- Ethylene Oxide

- Fluorine
- Acrylonitrile
- Hydrogen Sulfide
- Methyl Isocyanate
- Hydrogen Selenide
- Sulfur Dioxide
- Acrolein
- Arsine
- Compound 1080/1081
- Tetramine (TETS)
- Phosphine
Chlorine

- Common Toxic Industrial Chemical ("TIC").
- Why use it in war/terror?

Syrian army responsible for third chlorine gas attack, says UN inquiry

Activists accuse Syria regime of chemical attack in Aleppo
Chlorine

- **Density of 3.21 g/L.**
  - Heavier than air (1.28 g/L) sinks.
  - Concentrates in low-lying areas.
    - Like basements and underground bunkers.
- **Reacts with water:**
  - Hypochlorous acid (HClO)
  - Hydrochloric acid (HCl).
- **Mucus membranes and eyes have significant water.**
- **Penetrates into lungs.**
  - Caustic acute lung injury.
Treatment

- Primarily supportive.
  - Manage acute lung injury.
  - CPAP/BiPAP/ETI/ECMO

- Bronchospasm common.
  - Beta agonists + Ipratropium.
  - Nebulized lidocaine for coughing.
  - Nebulized sodium bicarbonate and steroids are controversial.
  - No role for prophylactic antibiotics.
Vesicants

- Include sulfur mustard (H, HD) and organic arsenical Lewisite (L).
- Primarily exert effects on:
  - Skin
  - Eyes
  - Lungs
• Mustard
  o Immediately absorbed by exposed surfaces.
  o Clinical effects may be delayed for hours.

• Lewisite
  o Causes immediate symptomatology.
Mustard Toxicity

Liquid

- Blister 10 μg
- Death (LD$_{50}$) 100 mg/kg

- LD$_{50}$ is equivalent to 20% TBSA.
- 50% TBSA therefore has 2.5 LD$_{50}$ doses.
  - Implications for MCI Triage.
Management

- Early decontamination - within 1 - 2 minutes - is the only effective means of preventing or decreasing tissue damage.
- Primarily supportive care.
  - BAL decreases systemic effects of Lewisite.

Sidell FR et al. 1997
• Myth: Treat vesicant injuries as burns.

• Reality: Fluid loss is not of the magnitude seen with thermal burns.

• Over-hydration using the Parkland formula has resulted in decompensation, including pulmonary edema.

Willems JL. 1989
Nerve Agents

- First synthesized 23 December 1936 by Gerhard Schrader, while looking for a safer pesticide than nicotine.
  - Organophosphates.
Nerve Agents

- 1st Generation - G (German) Series
  - High volatility, non persistent to semi-persistent
    - GA - Tabun
    - GB - Sarin
    - GD - Soman
    - GF - Cyclosarin

- 2nd Generation - V (Venomous) Series
  - Low volatility, persistent effect and liquid contact hazard
    - VE
    - VG - Tetram (Commercial insecticide sold as Amiton by ICI)
    - VM - Edemo
    - VR - R33, November, Russian VX
    - VX
• 3rd Generation - Novel or Atypical Series
  • Volatility between G and V agents. Semi-persistent to persistent effects.
    ▪ GV
    ▪ Novichok agents

• Non-OP - T Series
  • Related to Tetrodotoxin
    ▪ Saxitoxin (TZ)
Novichok Series

- **Newcomer** (“новичок”).
- Developed under Soviet program “FOLIANT”
- More than 100 agents.
  - Binary analogs 1980s-1990s
- 5-8 times more potent than VX.
- Novichok-5 (A-232) and Novichok-7 were most potent.
Physical Properties - Classic Agents

- Clear colorless liquid at RT
  - Not “nerve gas”
- At room temperature, most spontaneously volatilize.
  - GB > GD > GA > GF >> VX
- Penetrate skin and clothing.
  - Effects may be delayed up to 18 hours with dermal exposure.

Al Qaeda Video, Afghanistan
Primary Mechanism of Action

- Inhibit enzyme acetylcholinesterase (AChE).
- Result in ACh accumulation and continued stimulation of the target organ.
- Inhibition becomes permanent unless the agent is rapidly removed (“aging”).
Other Effects

- Directly binds to:
  - Nicotinic receptors
  - Cardiac muscarinic receptors
  - NMDA receptors

- Phosphorylates and inhibits Neuron Target Esterase.

- Antagonizes GABA neurotransmission.
Clinical Effects

- Effect organs with cholinergic receptors
  - Muscarinic
    - Smooth muscles
    - Glands
  - Nicotinic
    - Skeletal muscles
    - Ganglia
  - CNS

VX LD$_{50}$ - dermal
Muscarinic Effects

- **D** Defecation
- **U** Urination
- **M** Miosis
- **B** Bradycardia, Bronchorrhea
- **E** Emesis
- **L** Lacrimation
- **S** Salivation
Soman-Induced Intussusception


Fig. 1. Photo of a typical ileo-duodenal intussusception at 24 h following soman (135 µg/kg) in the guinea-pig. The arrows indicate the direction of the gastrointestinal tract. Int indicates the site of the intussusception.
Nicotinic Effects

- **Skeletal muscles**
  - Fasciculations
  - Twitching
  - Weakness
  - Flaccid paralysis
- **Other (ganglionic)**
  - Tachycardia
  - Hypertension
Cardiac Effects

3 phases:
1. Nicotinic Predominant - HTN and sinus tachycardia.
   - Sinus tach present in 35% of hospital admissions.
2. Muscarinic Predominant - Bradycardia, ST-segment changes on ECG (24% with ST segment elevation, 17% T wave inversion).
   - Bradycardia noted in 28%.
3. Arrhythmia Predominant - TdP, Sudden Cardiac Death
   - QTc > 580 msec associated with SCD.

Ludormisky et al 1983
Grmec et al 2004
Karki et al 2004
Schematic of Hemodynamic Effects of Nerve Agents - Swine Model

Data courtesy Defense R&D Canada - Suffield.
OP-Induced Delayed Polyneuropathy (OPIDN)

- Distal dying-back axonopathy.
- Due to phosphorylation of neuropathy target esterase (NTE).
  - 1-3 weeks after exposure.
  - Cramping pain in legs, paresthesias, motor weakness.
  - Pyramidal signs and symptoms may occur.

- Significant concern with Novichok agents.
Pediatric Effects

- Children may present differently from adults.
- Isolated CNS effects (coma) in absence of peripheral muscarinic effects.
- Absence of miosis in 43% of pediatric cases.
- Significant muscular weakness in the absence of SLUDGE secretions in 70-100% of cases.
Treatment
Atropine

- Treats muscarinic symptoms (DUMBELS).
- US auto-injectors contain ~2 mg atropine.
  - Severe intoxication: 3 auto-injectors and diazepam.
- Atropine 2 mg IV q 3 - 5 minutes
  - Titrate to a reduction in secretions and ventilatory resistance.
  - Do not titrate to pupils or heart rate.
- In severe intoxication, 10-20 mg of atropine may be required over first several hours.
Oximes

- Historically used to restore enzyme activity.
- Clinically noticeable in reversing nicotinic effects.
  - Oximes only useful if aging has not occurred.
  - For most nerve agents, the aging period is relatively long.
    - GD (Soman) ages in less than 2 minutes.
    - May not work for Novichok.
## Current Oxime Use by Country

<table>
<thead>
<tr>
<th>Oxime</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-PAM</td>
<td>USA, UK, France</td>
</tr>
<tr>
<td>Toxogonin (Obidoxime)</td>
<td>Norway, Netherlands, Germany</td>
</tr>
<tr>
<td>HI-6</td>
<td>Canada, Sweden, Czech Republic</td>
</tr>
</tbody>
</table>
## Relative Protective Effect of Oximes on Nerve Agent Poisoning

<table>
<thead>
<tr>
<th>Nerve Agent</th>
<th>2-PAM</th>
<th>HI-6</th>
<th>Toxogonin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (Tabun)</td>
<td>4.2</td>
<td>3.9 – 5.1</td>
<td>19</td>
</tr>
<tr>
<td>GB (Sarin)</td>
<td>23</td>
<td>67</td>
<td>59</td>
</tr>
<tr>
<td>GD (Soman)</td>
<td>2.1</td>
<td>3.1 – 6.5</td>
<td>2.0</td>
</tr>
<tr>
<td>GF (Cyclosarin)</td>
<td>2.6</td>
<td>31</td>
<td>2.5</td>
</tr>
<tr>
<td>VX</td>
<td>37</td>
<td>66</td>
<td>58</td>
</tr>
</tbody>
</table>

Protective Ratio = \( \frac{\text{LD50 Agent + Oxime}}{\text{LD50 Agent Alone}} \)

Data courtesy Defense R&D Canada - Suffield.
Auto-Injectors

- ATNA/DuoDote
  - Atropine 2.1 mg
  - 2-PAM 600 mg
  - Adult (> 40 kg)
Drug Shortages

- Drugs may be fine.
- Failures with needle propellant.
Convulsion Antidote Nerve Agent (CANA)

- Diazepam 10 mg
- Midazolam now approved for use.
- Recommended as an AED in severe intoxication.
Non-Cholinergic Interventions

- No effect on cholinesterase levels.
- Intralipid 20%
- Ketamine sedation
- Therapeutic hypothermia
  - Cooling skin decreases dermal absorption.
- Scavenger Enzyme Therapy
  - FBS-AChE acts as sponge.
- Goat-derived rhBChE
- Abzymes
  - Enzymatically-active antibodies
Nerve Agents and Intubation

- Nerve agents inhibit enzyme butyryl-cholinesterase (BChE).
- Responsible for degradation of succinylcholine.
- Prolonged apnea and muscle relaxation after use of succinylcholine in OP poisoning.
  - Range 1 - 7 hours reported.
- BChE also responsible for mivacurium metabolism.

Sener EB et al. 2002.
General Management
MARCH CBRNe Variant

- Massive Hemorrhage
- Airway
- Respirations
- Circulation
- Hypothermia/Head Injury
- Mask
- Antidotes
- Rapid Spot Decon
- Countermeasures
- Hypothermia
Tokyo Sarin Attack

- 10% of 1364 EMS personnel became victims due to Sarin off-gassing.
What Level PPE?

Survey of UK Health Care First Responders’ Knowledge of Personal Protective Equipment Requirements

Jan Ummacher, MD, PhD;³ Alexandra R. Bond, MD;² Valentine Woodham, MD;³
Anna Buckingham, MD;¹ Francesca Garnham, MD;² Andrea Brinker, MD³

Abstract

Introduction: An adequate level of personal protective equipment (PPE) is necessary when treating patients with highly infectious diseases or those contaminated with hazardous substances.

Methods: Following the National Institute for Health Research’s Research Centre (London, United Kingdom) approval, the authors of this study conducted a survey of specialists’ knowledge of the respiratory and skin protection requirements needed during a pandemic scenario with Advanced Life Support. Participant responses were compared to UK national recommendations and to a previous survey in 2019.

Results: A total of 93 specialists (9% Anesthetists, n = 33; 16 Emergency Medicine (EM), n = 21; and 1 Intensive Care Medicine (ICM), n = 20) completed 130 delivered surveys. The lowest knowledge of PPE requirements (24%) was found for Level C: Limited Skin & Limited Respiratory Protection.

Threat

- Vapor
- Gas
- Liquid/Splash
- Solid

PPE

- Level A
- Level B
- Level C
- Level D
3/30 Rule

- **Applies when:**
  - CBRN/Level A suits are not available
  - Structural firefighting PPE (Turnouts and SCBA)
  - Immediate rescue of known live victims
    - Can operate for 30 minutes
    - 50% “may experience increased sweating and muscle weakness 1-18 hours after exposure.”
  - Search for live victims
    - Limit exposure to 3 minutes.
PPE and Trauma

- PPE decreases visual field, depth perception, dexterity.
- Fall risk.
  - Spinal column injury from falling on SCBA pack.
- Hemorrhage risk.
  - High threat environment.
  - Single TQ is insufficient due to size/bulk of PPE.
    - Especially FF Turn-Out Gear.
Operational Concerns

- Subject sprays nerve agent on mayoral candidates.
- Has a firearm.
  - PD cannot enter/engage due to CBRNe threat.
  - FD cannot enter due to firearm threat.
- Break down silos!
Decontamination
Decontamination was only performed in 25% of patients.

- Inefficient manner.
- No PPE except surgical masks and latex gloves.
The Dilemma - Clean or Dead?
What is the Goal of Decontamination?

- Minimize the effects of contamination in order to:
  - Improve patient outcomes.
  - Protect health care providers.

- The goal is not simply to clean for the sake of being clean.
  - Clean and dead.
  - Dirty and alive.
  - Which is better?
The PRISM “Rule of Tens”

... rapid and effective completion of each stage of the incident response procedure yields a ten-fold reduction in the level of casualty contamination
When Should Decontamination be Performed?

- When a risk exists!
- Gases: Typically no risk other than off-gas.
- Vapors: Higher risk.
- Liquids: Wet vs Dry decontamination.
- Solids: Brush off.
How Soon?

- **AS SOON AS POSSIBLE!**
- Ideally less than 10 minutes.

- Initially clothes act as a barrier to contamination.
- As time goes on, clothes become a source of transfer of contaminant to skin.

*Figure 6: Relationship between effectiveness of decontamination and time post exposure [40].*
Why Patients Should Disrobe First

A: Disrobe followed by showering

B: Shower without disrobe

Figure 2: Photographs of residual skin contamination (indicated by green areas) on torso of volunteer following water shower decontamination. Removal of clothing before showering results in efficient removal of contaminant (A). In contrast, there is an increased spread and intensity of residual skin surface contamination when contaminated clothing is worn during showering (B).
Does Everyone Need Wet Decontamination?

Figure 4: Range of absorbencies (gram of oil absorbed per gram of test product) for materials that may be readily found in ambulances or the domestic environment. Data provided for illustrative purposes only and does not represent an endorsement of any particular type of product.
Figure 8: Salient features of the Primary Response Incident Scene Management (PRISM) process.
The Loaded Question

- If there is no way to ID/detect the chemical, how do you know when you have accomplished your decontamination goal?

- For TICs, 60 - 90 seconds is typically sufficient.
High Risk Agents

- Certain agents remain toxic even in microscopic amounts.
  - VX
  - Novichok
  - Biowarfare agents
- Nearly impossible to declare patient “clean” in a timely manner.
- After decon, transfer patient wrapped up and “dirty”
  - Transfer vehicle is considered dirty.
  - Crew in PPE.
Vehicles buried in landfill site after novichok poisonings in Wiltshire

The secure burials in a hazardous waste landfill site would pose "absolutely no risk to the public", says a Defra spokesman.

In March, military personnel removed two ambulances from Salisbury ambulance station.
Man Down Procedure - Can You Do an Emergency Doff?
Some Final Words of Wisdom

“If 1 person in a room has a seizure, think epilepsy. If more than 1 person has a seizure, get the hell out of there!”

Colonel (Ret) Edward Eitzen, M.D.
Any Questions?