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EDITORIAL COMMENT

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Commentary on Chemical Warfare Agents and Current Threats

Kimyasal Savaş Ajanları ve Güncel Tehditler Hakkında Yorum

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The fast development of chemical industry during the 20th century, unavoidably promoted the large-scale introduction of chemical warfare agents (CWAs). There is a global control system of CWAs based on Chemical Weapons Convention, but still CWAs pose a persistent global security threat to civilian population. The latest issue of Lokman Hekim Health Sciences features an extensive narrative review on CWAs or chemical weapons, authored by Dr. Kenar.[1] This review comprehensively examines the various aspects of chemical weapons, including historical applications, their mechanisms of action, antidotes and medical management strategies. Türkiye is located in a region where conflicts between nations are intense. In this respect, this review is also important in terms of raising awareness.

The use of chemical agents as weapons dates back to 431 BC, when sulfur compounds were deployed during the Peloponnesian War. More recent historical instances include the widespread use of chlorine gas during World War I and the introduction of nerve agents by Nazi Germany in 1943. Despite the prohibitions outlined in the 1925 Geneva Protocol, several countries have continued to employ chemical weapons, as seen in the Italian invasion of Ethiopia (1935), Japanese chemical attacks on China (1937). The Vietnam War also witnessed the extensive use of chemical agents, further highlighting their devastating impact. Herbicides were also used as CWA, for example, from 1962 to 1971, the USA government sprayed nearly 75 million liters of herbicides (Agent Orange) during the Vietnam War.[2]

Chemical weapons are broadly categorized into four major classes based on their mode of action:[3]

- Nerve agents: Inhibit acetylcholinesterase, leading to neuromuscular paralysis (e.g., tabun (ethyl-N-dimethylphosphoroamidocyanidate, code: GA), sarin (isopropylmethylphosphonofluoridate, GB), soman (pinacolyl methylphosphonofluoridate, GD), VX (o-ethyl S-[2-(diisopropylamino)ethyl]methylphosphonothiate)).
- Blistering (vesicant) agents: Cause severe skin, eye, and respiratory irritation (e.g., sulfur mustard (2,2′-dichlorodiethyl sulfide, HD), nitrogen mustard (2,2′-dichloro-N-methyldiethylamine, HN-1), Lewisite I (dichloro(2-chlorovinyl)arsine, L1).
- Pulmonary agents: Induce respiratory distress by damaging lung tissue (e.g., phosgene (CG), chlorine (CL).
- Cyanogenic agents (cyanides): Disrupt cellular respiration and oxygen utilization (e.g., hydrogen cyanide, cyanogen chloride).

In addition to these four groups, there are incapacitating agents that cause to temporary disability, disorientation, or unconsciousness rather than kill.[1] However, these agents can also kill if used in a high enough dose.

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Potential sources of exposure to CWAs include accidental releases from military stockpiles, industrial accidents, direct military deployment, wars, and acts of terrorism. Among these, cyanide and cyanogenic agents are particularly lethal due to their impact on cellular respiration and oxygen utilization, ultimately leading to cytotoxic anoxia. Cyanide exhibits a strong affinity for ferric iron (Fe^{3+}), inhibiting mitochondrial cytochrome c oxidase (Complex IV), which results in cellular asphyxiation and death. Treatment strategies for cyanide poisoning primarily focus on providing an ample supply of oxidized iron to outcompete cytochrome oxidase for toxin binding.

Other chemical warfare agents, such as nerve agents (e.g., tabun, sarin, VX), vesicants (e.g., mustard gas, Lewisite), and pulmonary agents (e.g., chlorine gas, phosgene), have distinct mechanisms of action that result in severe physiological damage. Nerve agents inhibit acetylcholinesterase, leading to neuromuscular paralysis, while vesicants cause severe tissue damage. Pulmonary agents disrupt respiratory function, leading to fatal pulmonary edema.[3]

Rapid identification of chemical warfare agents is essential for timely medical intervention. Automated instrumentation, including chromatography – mass spectrometry based techniques (GC-MS, LC-MS, tandem MS) with various detection systems, and ion mobility spectrometry allows for have been employed for the definitive identification of nerve agents and organophosphate pesticides. Among these, vesicants such as sulfur mustard and Lewisite have been extensively studied using GC-MS for biomarker detection, including alkylation adducts formed with hemoglobin, serum albumin, and DNA. Determining cyanide concentrations in biological samples is crucial for biochemical confirmation and post-antidotal treatment assessment. Blood samples for cyanide analysis must be stored in sealed containers to prevent degradation or contamination. Analytical methodologies such as head-space gas chromatography and GC-MS have been utilized for the detection of cyanide and its derivatives such as thiocyanate in biological specimens.[3–5]

However, these procedures time-intensive because of the complexity of their procedures and time-consuming derivatization reactions.[4,5] Therefore, studies are being carried out for new easier methods. Indeed, studies are being conducted with fluorescent probes.[6] There are also simple and rapid semiquantitative "field methods" on test papers for blood and water cyanide.[3,7,8] Serum cholinesterase activity measurement is a simple and established approach for assessing acute and chronic exposure to these compounds. Advancements in biosensors and portable analytical devices have further improved the capability of field diagnostics. Techniques such as enzyme-linked immunosorbent assays (ELISA) and real-time polymerase chain reaction (PCR) have also been explored for rapid detection of biological and chemical agents in emergency settings.

Given the potential for mass casualties and widespread panic in the event of a chemical or biological attack, healthcare institutions must be well-equipped to manage such crises. Clinical laboratories play a crucial role in the rapid diagnosis and identification of toxic agents, which is fundamental for prompt medical intervention. Providing educational materials and conducting seminars on chemical and biological warfare agents can enhance preparedness within healthcare institutions. Furthermore, clinical laboratories should secure funding from local authorities to support the procurement of specialized equipment, reagents, and trained personnel. Ensuring adequate protective measures for laboratory personnel handling hazardous materials is imperative. Many hazardous-material response teams are equipped with Level A personal protective equipment, which should also be provided to local laboratory personnel involved in handling and analyzing suspected toxic agents. In cases of suspected bioterrorism, laboratories must adhere to stringent biosafety protocols. The implementation of high-containment biosafety level (BSL) laboratories and the establishment of rapid communication channels with governmental agencies are crucial components of an effective response strategy.[9]

The Chemical Weapons Convention (CWC), signed by Türkiye in 1997, strictly regulates the production, stockpiling, and use of chemical weapons. According to the CWC, the use of tear gas in enclosed spaces, at close range, or in high concentrations constitutes a violation of international law.[10] Additionally, the 1996 United Nations resolution calling for the prohibition of tear gas underscores the global effort to mitigate the humanitarian impact of chemical agents.

The persistent threat posed by chemical warfare necessitates continuous advancements in detection methodologies, medical countermeasures, and laboratory preparedness. Clinical laboratories play a pivotal role in both the immediate medical response and long-term surveillance of chemical agent exposure. Strengthening international collaborations and regulatory frameworks remains essential in mitigating the risks associated with chemical and biological warfare. Future research should focus on novel antidotes, rapid detection technologies, and improved decontamination procedures to enhance global security against CWA threats.

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