Chapter

Assaults with Highly Toxic Substances in Public Spaces: Preparedness in Lessons Learnt from Precedent Cases

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Abstract

The use of chemical substances in terrorist scenarios is to be feared everywhere. Especially after the events that have attracted attention in recent years such as the incident of a Sarin assault on Tokyo subway on March 20th 1995. In addition, the attacks with Novichok on the former Russian double agent Sergei Skripal in Salisbury, March 4th 2018, as well as on the prominent Russian opposition leader Alexei Navalny during a flight from Tomsk to Moscow on August 20th 2020 affected not only paramedics but also civilians in public areas. In order to collaterally protect civilian populations in the event of an emergency, the poisoning pattern (toxidrome) must be recognized as quickly and reliably as possible. Training on the relevant agents is needed and provision of necessary rescue equipment (antidotes) in prepared facilities is urgently required. In the event of a terrorist-motivated chemical attack, physicians from the Public Health Service (PHS) will foreseeably play a key role in communicating with decision-makers and the public as part of a competency network. As part of their preparation, the participants in the Bavarian Public Health training course are instructed in clinical symptomatology, toxicodynamics and therapy in the event of exposition to the most menacing, highly toxic chemical substances like organophosphorus (OP) compounds or vesicants such as Sulfur Mustard.

Keywords: chemical substances, terrorism, antidotes, Public Health Service, poison center

1. Introduction

The recent use of Sarin in Syria [1], the assassination of Kim Jong-Nam with VX in Malaysia [2] and the attack on Sergei Skripal with Novichok [3] underscore the persistent threat posed by organophosphorus (OP)-based nerve agents [4]. Since the 1930s, when Gerhard Schrader first discovered highly toxic OP compounds during

pesticide research, there has been an ongoing effort to improve medical countermeasures and methods for early diagnosis of nerve agent poisoning. Upon exposure to an OP nerve agent (OPNA), the critical enzyme acetylcholinesterase (AChE) becomes inhibited through covalent binding of the agent to the active site serine. This inhibition results in the accumulation of the neurotransmitter acetylcholine at cholinergic synapses, followed by a cholinergic crisis owing to the overstimulation of cholinergic receptors, resulting in muscarinic and nicotinic signs. Among the muscarinic ones are salivation, lacrimation, urination, diarrhea, gastrointestinal distress and emesis; among the nicotinic ones are a broad spectrum of striated muscle dysfunction, including muscle weakness, fasciculations, with finally flaccid paralysis because of permanent depolarization. Central nervous system (CNS) manifestations enfold the impairment of respiratory drive, the loss of consciousness and seizures. Inhibited AChE may reactivate spontaneously, be deliberately reactivated by the administration of an oxime or undergo an aging reaction by losing an alkyl group—thus being permanently inactivated. Immediate treatment with a muscarinic receptor antagonist and an oxime is the current strategy to improve the survival of poisoned patients. However, the therapeutic effectiveness of currently licensed oximes is limited, e.g., by their insufficiency in reactivating AChE inhibited by certain nerve agents (e.g., Tabun), the inability of oximes to cross the blood-brain barrier and an aged form of AChE that cannot be reactivated [5, 6]. A meaningful part of the above-mentioned preparedness would be to prepare also physicians from PHS in terms of content for the case of an assault with highly toxic chemical substances. Although they would not be part of the responsible rescue team there is likelihood for them to be questioned as experts on the risk of the exposed population from mayors or district administrators. For such a case of emergency, a bioterrorist assault for example, it is to fear that major stress for the clinical supply system would arise from worried well who could multiply the number of truly injured people. This was already demonstrated by the precedent assault with Sarin on the Tokyo subway on March 20th 1995 [7]. For a necessary development of information materials and behavioral codes for the public during and after an assault with chemical substances, the PHS may account for the preservation of civil society and relief of clinical care from worried well [8]. Subsequently, there is some introductive information compiled on known substances like nerve agents, vesicants or opioids and experiences from incidents in recent years.

2. Nerve agents

One of the most feared chemical substance groups, nerve agents, blocks the organisms' cholinesterases, specifically the serums' pseudocholinesterase (butyrylcholinesterase (BChE)) whose activity is crucial for assessing the course of intoxication. It behaves like the neuronal cholinesterase, whose inhibition determines the patient's clinical picture. After elimination of the nerve agent's "leaving group" (X-group) (**Figure 1**), which determines the speed of the effects' onset, acetylcholinesterase (AChE) will be inhibited by phosphorylation of a specific serine residue in the enzyme's esteratic center. This reaction occurs more or less quickly after exposure to nerve agents. The loss of AChE function causes the complete peripheral, autonomic and central nervous systems to be permanently overstimulated, leading to a cholinergic crisis. Understanding the further biochemical reaction in nerve agent poisoning is crucial for assessing therapeutic options. The loss of alkyl residues (R1, R2) (**Figure 1**) from the nerve agent-cholinesterase complex is called "aging" and results

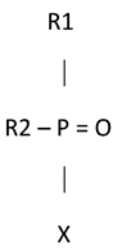

Figure 1.
Structural formula by Schrader.

in an irreversible, non-influenceable inhibition of AChE. Such a condition occurs within minutes of exposure to Soman (GD) (the half-life of Soman-AChE-complex is about 2 minutes), whereas it takes considerably longer after exposure to Sarin (GB) (half-life of 3 hours) and VX (half-life of 30 hours).

The organophosphorus substances were first synthesized by the politically aligned German dye industry, originally in search of insecticides before and during World War II. Gerhard Schrader synthesized Tabun (GA) in 1936 and Sarin (GB) in 1938, while Richard Kuhn, Nobel laureate in Chemistry in 1938, developed Soman (GD) in 1943. Further developments followed in England by the group surrounding British chemist Ghosh with VX in 1949. Its production rights were transferred to the US. The development of additional isomers followed in Russia (Russian VX (RVX)) and China (Chinese VX (CVX)). VX and its analogs belong to the so-called V (venomous) substances, which are phosphorylated thiocholine compounds without electron-donating groups, making them resistant to hydrolysis. This characteristic, combined with their very low volatility, ensures that these substances can be absorbed through unprotected skin into the bloodstream. Novichok was developed in the former USSR's "FOLIANT" project in the 1970s as a third-generation nerve agent with an organophosphorus structure, leading to at least four so-called A-agents (Substance-33, A230, A232, A234), with undetermined structures that could potentially be used in binary systems (Novichok-#, -5, -7), which are likely 5–10 times more effective than VX. The lethal dose 50% (LD50) of Novichok substances shall come up with 0.22 μg/kg that of 2-(dimethylamino)ethyl N,N-dimethylphosphoramidofluoridate (VG), a further new nerve agent of fourth generation [9]. Regarding therapeutic approaches, there are no differences from other organophosphorus compounds. After decontaminating the skin, the administration of anticholinergics Atropine, anticonvulsants (Diazepam) and oximes is indicated. However, the use of oximes would have a limited nucleophilic effect due to the A-agent already being complexed with AChE. Sarin and Soman are predominantly volatile substances, so their incorporation is expected mainly through inhalation. Cyclosarin (GF) and Tabun have more persistent properties, so their uptake can also occur through the skin. VX, in contrast, primarily develops its effects through skin contact.

2.1 Nerve agents' effects

In the early phase or in cases of minor poisoning, sympathetic symptoms are present due to preganglionic cholinergic transmission, with tachycardia and hypertension being predominant. As the parasympathetic response predominates, the typical symptoms of organophosphorus poisoning emerge, including hypersecretion of bronchial glands, bronchial muscle contractions, profuse sweating, salivation and

tearing due to muscarinic overstimulation of exocrine glands. In the somatomotor system, nicotinic overstimulation causes symptoms such as eyelid tremors, contractions of facial muscles and muscle fibers, eventually leading to flaccid paralysis due to continuous depolarization. In the central nervous system (CNS), a cholinergic crisis causes dizziness, restlessness, speech disorders, loss of motor coordination, seizures and coma via muscarinic and nicotinic pathways. Fatality can result from central respiratory failure and pulmonary edema, which in severe cases may be accompanied by cardiovascular collapse.

Given this, it is essential to involve physicians from Public Health Service (PHS) during a terrorist chemical assault. While they may not directly care for casualties, they can be consulted by authorities and the press as experts on existing threats to the general population. In emergencies, such as the suspected bioterrorist attacks like those during New York City's 9/11 attacks and its extension to Afghanistan [8], there is concern that the number of casualties could increase due to the "worried well," who might misinterpret the danger and add pressure to clinical systems, as seen in the 1995 Tokyo Sarin attack. To effectively handle such situations, including public information and rules of conduct, PHS can help maintain a functioning civil society at the regional level, manage the concerns of the worried well and ensure access to specialized staff for diagnosis and poison information, thus preventing unnecessary visits to clinical centers [6].

The "worried well" often overestimate their exposure to poison, influenced by media coverage of actual victims, which they cannot differentiate due to fear, lack of experience and knowledge. Information materials should be distributed in advance to guide people on how to act in situations where they perceive potential danger [8].

The most important measures in an emergency are ensuring that emergency services are trained to recognize the signs and symptoms of life-threatening events in which poisoning is not only possible but highly likely due to the circumstances. Securing the availability of crucial supplies (antidotes, decontamination materials, personal protective equipment (PPE)), and the transfer of affected individuals to more specialized institutions, if necessary is vital. It is also important to secure specimens from affected patients for poison detection and forensic examination. On-site diagnostic capabilities, such as detecting acetylcholinesterase (AChE) activity or spot contamination, should be available, and action teams should be equipped with self-protection gear.

2.2 Experiences of assaults with nerve agents

Lessons to be learnt in the management of nerve agents arose from the Japanese Sarin attacks carried out by Aum Shinrikyo on June 27th 1994 when the politically motivated cult released about 20–30 kg of Sarin through the window of a converted delivery truck and spread the substance over a residential area in Matsumoto to poison three district court judges, thus trying to preempt an anticipated unfavorable ruling.

Some 600 people were exposed, 253 sought medical attention at outpatient clinics. The majority suffered from decreased visual acuity and miosis (n = 57). There were 58 patients admitted to hospitals and all recovered. Seven casualties living close to the release of the chemical died before getting to the hospital and the judges, who were the primary targets, survived. The death toll from the assault would probably have been higher if the release of the Sarin had been more efficient.

On March 20th 1995, members of the same sect released an estimated 4.5 L of dissolved Sarin on five central line subway trains in Tokyo during the morning rush hour. First emergency calls reached the fire department within 20 minutes from 15 different stations. Authorities at first did not understand that the emergency had a single cause. Arriving at the scene, rescue teams found commuters stumbling about with impaired vision, struggling to breathe. Casualties littered the subway station exits, some foaming at the mouth, some vomiting and others convulsing. Inside subway stations and near the exits, rescue teams began to triage victims and offer medical assistance, although they administered no drugs and did not intubate serious cases at the scene. Nor did they decontaminate the victims, but took the most seriously affected patients to hospital.

Over 5000 "casualties" sought medical attention, 984 persons were moderately and 54 persons severely poisoned, 12 died [7].

Making a correct diagnosis was challenging due to discordant vegetative signs (tachycardia on one hand but miosis on the other hand) in the course of early or mild intoxication. False diagnosis occurred based on suspicion (e.g., Acetonitrile) in an unclear and confusing situation, complete with an obvious lack of necessary information and means for detection.

The Sarin assault in Tokyo is the most well-documented case of mass intoxication. Leading symptoms consisted of miosis (99%) with a severe headache (83%), dyspnea (70%) and nausea (67%). Further emesis, weakness, fasciculations and obtundation were visible. Some classic muscarinic signs like sweating, salivation and lacrimation were astonishingly less observed. The miosis was caused by local contamination of the eye.

In the cases of Navalny and Skripal, two further poisoning incidents with nerve agents (see further down), unconsciousness occurred soon after a short phase of nausea. While the suppression of cholinesterase by volatile nerve agents endures for only a short time (1 day), it lasts for several days in fluid and solid substances like VX and Novichok. With Soman and Tabun, the application of an oxime remains ineffective, whereas with Sarin, VX and also Novichok an early application might be helpful. In Navalny's case, it occurred too late [5, 10].

In Tokyo, most affected individuals were taken to hospital without prior on-site decontamination, which should have been done urgently to avoid exposing hospital staff to secondary toxin exposure. The same problem emerged due to the non-availability of personal protective equipment (PPE) in hospitals, and therefore adequate decontamination procedures could not be conducted there. Thus, 23% of 472 staff members in St. Luke's Hospital complained of acute symptoms of secondary toxin exposure but none of them got any treatment. Besides that, a lack of essential antidotes (Atropine, Oximes) was registered at the scene [7].

2.3 Experiences from life-threatening, politically motivated incidents with nerve agents

On February 13th 2017, two women both rubbed the face of Kim Jong-Nam, half-brother of the North Korean dictator, at Kuala Lumpur International Airport, Malaysia for 7 seconds with four low-toxic starting substances that reacted to VX on his eyes and skin. This led to his death within 20 minutes. Although the two assassins had not worn gloves, they were little affected by the poison. The chemical analysis by the Malaysian government indicated that Kim indeed was killed by VX.

VX was likely synthesized from several precursor compounds applied sequentially by the two women involved in the attack. The binary VX system developed by the U.S. Army consists of two components: QL (isopropyl aminoethylmethyl phosphonite) and rhombic sulfur. However, Malaysian police reported that QL was not detected on either of the women's hands or on Kim Jong-Nam himself.

A key observation was that the chemical compounds identified from the three individuals—the two attackers and the victim—were all different, which strongly suggests the use of a binary nerve agent system. This is particularly compelling, given the stark differences between the substances found on each woman. If preformed VX had been used instead of a binary system, one would expect the same compound to be present on both women.

On the Indonesian woman's T-shirt, ethyl methylphosphonic acid was detected. Meanwhile, samples from the Vietnamese woman's T-shirt and fingernails contained 2-(diisopropylamino)ethyl chloride, 2-(diisopropylamino)ethanethiol and bis(2-diisopropylaminoethyl) disulfide. These findings support the hypothesis that VX was formed directly on Kim's face after the second woman applied the final component with her palm.

Kim's complaint of eye pain shortly after the attack suggests that the nerve agent entered his body through ocular tissues, causing both immediate irritation and rapid systemic absorption. This could explain his death within 20 minutes of exposure. It is likely that a lethal dose of VX was absorbed through the mucous membranes of his eyes [2, 11, 12].

On March 4th 2018, Sergei Skripal, a former Russian double agent, and his daughter, were poisoned with Novichok (Engl. "newcomer") in Salisbury by touching a primed door handle. They both collapsed on a bench close to the restaurant where they had eaten. The cause was not immediately obvious but it was recognized rapidly that they had been exposed to some toxic substance. A policeman was also exposed to what appeared to be the same substance while helping the Skripals. He was initially discharged from the hospital, but his condition deteriorated at home and he was readmitted there. With treatment, the three patients recovered, the Skripals were however discharged at least 2 weeks later because of their stronger exposition. Although 46 members of the public presented themselves at the hospital expressing concern and a further 131 people had been identified who could potentially have come into contact with the nerve agent, the Consultant in Emergency Medicine at the Salisbury NHS hospital stated that nevertheless no one other than the known three patients had needed treatment. On March 7th 2018, it was announced by the then Prime Minister (PM) that the Skripals had been exposed to a "nerve agent" and on March 12th that this was a Novichok nerve agent. This finding by the Defense Science and Technology Laboratory (DSTL), Porton Down was confirmed independently by the Organisation for the Prohibition of Chemical Weapons (OPCW), The Hague, on collected environmental samples. A woman, who found the used transport vessel in nearby Amesbury some months later, mistook its content and used it as a perfume, which caused her death from severe intoxication 8 days later [3].

On August 20th 2020, 44-year-old Alexei Navalny, a well-known Russian opposition activist, who was previously healthy suddenly became confused and began to sweat heavily on a domestic flight within Russia approximately 10 minutes after departure; he vomited, collapsed and lost consciousness. After an emergency landing, the man was admitted to a local hospital in Omsk, Siberia, approximately 2 hours after symptom onset. According to the discharge report, the patient presented comatose with hypersalivation and increased diaphoresis and was diagnosed with

respiratory failure, myoclonic status, disturbed carbohydrate metabolism, electrolyte disorders and metabolic encephalopathy. Therapeutic measures included intubation, mechanical ventilation and unspecified drugs for symptom control and neuroprotection. On August 22nd 2020, the patient was transferred by German air ambulance to the Charité University Hospital in Berlin at the request of his family. Severe poisoning with a cholinesterase inhibitor was subsequently diagnosed. Two weeks later, the German Government announced that the Institute of Pharmacology and Toxicology of the German Armed Forces in Munich, designated by the Organization for the Prohibition of Chemical Weapons (OPCW), had identified an organophosphorus nerve agent from the Novichok group in blood samples collected immediately after the patient's admission to Charité, a finding that was subsequently confirmed by the OPCW [10].

Mr. Navalny, who returned to Russia pretty directly after his discharge from the university hospital in Berlin, was immediately arrested at the airport because of alleged treason and finally died on January 16th 2024 in a prison in Siberia's northern polar circle from unknown reasons.

2.4 Nerve agents' poisoning effects and treatment

Nerve agents block the cholinesterases of all organisms by phosphorylation and thereby lead to a cholinergic overstimulation of the vegetative nervous system, the so-called cholinergic crisis. The inhibition of the neuronal cholinesterase determines the clinical picture of exposed patients, which merges into a reactivation-refractory, virtually irreversible inhibition depending on differences in time latency of the aging of poison-enzyme-complexes. This may lead to pre- and postganglionic caused discordant vegetative signs (e.g., miosis versus sympathicotonic vital parameters), which can cause clinical confusion among the physicians responsible for the first view on the case. Point-of-care devices for detection of erythrocyte acetylcholinesterase (EryAChE) are generally available and can ease diagnostic procedures considerably. They help to confirm a clinical suspicion of intoxication with nerve agents so that an adequate therapy can be initiated within minutes. Therefore, rescue teams should have them at hand. Initially, Atropine is able to treat and secure respiration and circulation by blocking muscarinic acetylcholine receptors. Starting with 2 mg, the dose can be doubled depending on patient's response, although 10 mg already constitutes a fairly high dose above which overdosing should be avoided. The dose for affected children has to be adapted critically, according to their ages or, if known, weight (0.02–0.1 mg/kg).

The control of cerebral seizures by an appropriate dose of Atropine is not possible. For this purpose, Diazepam 10–20 mg should be administered intravenously and repeated as necessary, usually once or twice, maximum three times per day under stationary conditions only.

Atropine has no influence on the functional paralysis of the respiratory muscles caused by nicotinic acetylcholine receptors, which is why attempts should be made to restore the neuromuscular transmission by application of an acetylcholinesterase reactivator. This approach at all synapses, also the parasympathetic ones, should help to save a large amount of Atropine doses. If this approach is effective it is also highly efficient, though subject to substance-specific limitations. As, for example, the Soman-AChE-complex ages within minutes and reactivation is no longer achievable after a short time. In addition, the currently known and available oximes, Obidoxime and the less effective Pralidoxime, show no broadband effect on all

relevant organophosphorus substances and pesticides acting in the same manner. A causal therapy is therefore not available for all substances. In the case of mass poisoning with Sarin/VX however, a reactivation could still be possible within hours. In cases with longer persisting substances with a prolonged cholinergic crisis, a continual atropinization (clinical criteria: free respiratory sounds on auscultation, heart rate > 80 beats/min, pupils>pinpoint, dry axilla skin, blood pressure > 80 mmHg) of exposed people can be necessary. In the event of an emergency, sufficient amounts of antidotes for several hundred victims must be held available in depots. Their use on severely poisoned persons in the field is made more difficult for the emergency services due to their obligation to wear protective suits. Recommendations in this regard are therefore discussed in a controversial manner but seem possible to implement with repeated training of the personal while wearing protective equipment. This should be held available at all disposable rescue centers. If reactivation fails, severely affected patients have to be ventilated mechanically until spontaneous respiration sufficiently recovers. An orientation of approximately 20% of normal butyrylcholinesterase (BChE) activity as reference for spontaneous recovery is only a rough indicator. Nevertheless, an inclining BChE activity shows a decreasing inhibition. The preferred surrogate parameter for neuromuscular transmission is EryAChE, which corresponds to neuronal AChE but its analysis is not readily available. This should be improved urgently for the case of an emergency. Decontamination by disrobing should be initiated before a transfer or at least before admission to hospital followed by showering in special decontamination units. Hospitals should also be prepared to proceed in the same manner with patients who self-present because adequate protection for their staff and facilities is of the highest importance [13].

2.5 Management of antidotal treatment in severe nerve agent intoxication

Atropine binds competitively to all muscarinic receptors without activating them. Therefore, it is the optimal means for replacing acetylcholine from these receptors and eliminating parts of the toxic effect. The nicotinic effects however stay unaffected, which means that the central nervous, ganglionic and muscular nicotinic effects remain after Atropine administration. Furthermore, patients can exhibit severe nicotine poisoning and therefore remain in need of ventilation and sedation. The most important life-saving effects of Atropine are the relief of bronchial spasms, bronchorrhea and bradycardia, raising the threshold for cerebral seizures and a favorable effect on the circulation. It should be dosed at 2 mg intravenously and its dose doubled every 5 minutes dependent on the patient's clinical response. In mass poisoning, the dose can only be given intramuscularly. The usual maintenance dose is 2 mg per hour. A sign that is easy to monitor is the pupil size, which is practical at the beginning of the poisoning when the pupil should only be of an average size. In the further course of treatment, pupil size is influenced by different sedatives and becomes less reliable for the assessment of the correct Atropine dose. More important than pupil size are, of course, the cardiovascular parameters that serve as a control for the Atropine dosage. A heart rate of 80–100 beats/min should be aimed for. However, this parameter becomes less valuable when, as it is very often the case, emerging pneumonia with the development of fever and tachycardia occurs. In this situation, the assessment of bronchorrhea is suitable for dosage control: there should be no more spasticity and crepitation on auscultation and little or no secretions. This parameter, too, becomes unreliable in the long term due to the pneumonia, which itself leads to secretions and crepitations. Beyond that, the assessment of diaphoresis, salivation

and bowel sounds can be used. Again, bowel sounds are not very consistent as they appear to respond to lower doses of Atropine than the other parameters. The remaining signs are considered to be diaphoresis and salivation. The cessation of the former can best be examined under the axilla, the latter by suction of the salvia in the mouth. Besides finding the optimal dosage, there is a further problem with atropinization. The gastrointestinal tract reacts most sensitively to Atropine, which can induce constipation on a relatively low dose of it. It also seems that adaption phenomena can arise, leading to a kind of "rebound" when stopping the Atropine therapy: This means that clear cholinergic signs can occur, even though no poisoning persists. Such a phase can be tolerated in a relaxed manner if the butyrylcholinesterase (BChE) or erythrocyte AChE (EryAChE) has already been increased [13].

Unfortunately, oxime antidotes do not act equally in all poisonings with phosphororganic toxins. In rapidly aging substances like Soman and dimethyl organophosphates, they work only when used very early after exposition. After sometime, reactivation is no longer possible due to the loss of the alkyl chains from their benzene rings. For this case, there are autoinjectors available, containing Atropine and an oxime, to improve the prognosis of exposed and symptomatic victims. In contrast, reactivation is successful with diethyl-organophosphates and several nerve agents, which split only slowly with aging half-lives of about 3 hours (Sarin) and some 36–40 hours (VX, diethyl-organophosphorus compounds). As the causative phosphororganic substance is usually unknown at the beginning of the poisoning, Obidoxime 250 mg should always be administered as a bolus as early as possible and be continued as an infusion at 30 mg/h or 750 mg/day. The first step of the oxime-induced reactivation is the additional binding of the oxime via a nitrogen atom to the phosphorylated acetylcholinesterase (AChE). This first step is dependent on the concentration of the reactivator and follows a dose-effect relationship. The second step describes the original reactivation. The oxime thereby escapes from the enzyme together with the phosphoryl residue of the toxin, a phosphoryloxime is formed and the serine residue of the AChE is released. This second step always takes place at the same rate, independent of the concentration of the oxime. Increasing the oxime dose therefore remains ineffective. A continuous increase in the dose should therefore be avoided but a concentration of 10–20 μmol/L Obidoxime in serum should be maintained long enough for maximal efficacy. Thereby, the effectiveness of oximes in severe poisonings with phosphororganic compounds is limited. In such cases, the inactivation of AChE by organophosphorus compounds may be faster than the reactivation by the oxime. Because this cannot be predicted in individual cases, a standardized procedure should initially be applied in all poisonings [13, 14].

To control the seizures triggered by nerve agents, benzodiazepines are effective anticonvulsants. Diazepam 10–20 mg should be administered intravenously and repeated as necessary under medical supervision and readiness for intubation. An alternative is Midazolam 10 mg, then a repeated dose of 10 mg after 10 minutes if required, but it offers no advantages over Diazepam [7].

3. Vesicants (blister agents)

The most important blister agent is Sulfur Mustard, a simple chemical substance called dichlorodiethyl sulfide. Various other names are S-Lost after the names of the two German chemists Lommel and Steinkopf who first proposed its suitability for widespread use as chemical warfare agent, and Yperit named after Ypern, the Belgian

site of its first use during World War I on July 12th 1917. Under normal environmental conditions, sulfur mustard is a fluid, which is why it has to be deployed as an aerosol to become maximally bioavailable, though it is questionable if this advanced technology was conceivable in Gulf War I or even World War I. Mustard gas is irritating to the eyes, skin and bronchial mucous membranes, manifesting itself, dependent on the concentration of poison, with a time latency of some hours. Initially, it reacts highly sensitively on the conjunctiva with lacrimation and light sensitivity, irritation, eye-lid spasms and pyogenic conjunctivitis. The skin shows rubor and edema with severe pruritus, which after prolonged or severe exposure transitions into painful, fluid-filled vesicles that are fully developed after 12–24 hours and which can lead to deep pyogenic ulcers. The susceptibility of the skin increases with the density of the sweating and sebaceous glands and typically shows affected areas in juxtaposition with discoloration. Initial respiratory symptoms are catarrhal disturbances, dry throat, hoarseness and aphonia, followed by purulent bronchitis and bronchopneumonia. They can also be accompanied by the formation of pseudomembranes and obstruction of the airways. Immunosuppression caused by hematopoietic failure in the bone marrow can contribute to the death of patients. Due to the lack of a specific antidote, the first step in the treatment chain consists of a careful decontamination of the affected persons using appropriate self-protection measures by the rescue team (protective suit, special gloves, boots, breathing mask). Skin lesions caused by Sulfur Mustard should be treated as burns that are complicated by a reduced wound healing. Ideally, the body surface should be dabbed with a paste containing hypochlorite early on, eyes must be flushed with water or 2% sodium bicarbonate liquid and the systemic effect can be avoided by infusion of sodium thiosulfate liquid, but this is only effective within 20 minutes of exposure. Clearing the bronchial system by tracheotomy and bronchoscopic debridement can save the victim from suffocation. Secondary infections have to be treated by antibiotics locally and systemically, according to the microbial sensitivity testing [5, 13, 15–17].

3.1 Experiences in poisoning with vesicants

The devastating effect of Sulfur Mustard has been known in Europe since World War I. Since then, severely wounded Iranians from the First Gulf War have also been treated in Germany and other parts of Europe. There were only a few fatal poisonings—possibly a selection bias in patients deemed fit enough to be transferred to Europe—but severe and permanent skin and tracheal disorders were observed. In these cases, enough time was available to provide medication, decontamination, repeated wound dressings and to take general care of those affected, if necessary over several weeks in hospital. However, in the case of a more severe involvement of the lungs, the prognosis could have been worse. The effective management of multiple assaults can obviously be very critical and may also lead to a burden of a country's health system in the long term [16, 17].

In mass poisoning, there will be an enormous workload on the hospitals that could interfere with the care of other patients. Sequelae on the lungs and eyes were common with obstructive pulmonary disease and secondary blindness.

4. Opioids

After the occupation of a musical theater in Moscow by Chechen terrorists on October 26th 2002 and the ensuing hostage rescue attempt by Russian authorities,

the undisclosed use of inhalative Carfentanil and Remifentanil via the ventilation system of the building led to the death of 127 (16%) of the 800 hostages in the theater and of at least 33 hostage-takers. All suffered from an undetected opioid intoxication, although classical signs (unconsciousness, respiratory depression, pinpoint pupils) were present. The Russian government had not revealed the used composition of the inserted aerosol, in public it was even presumed the application of highly toxic warfare compounds like Sarin, VX or BZ. After laboratory-analyzed findings of clothes and blood samples of two British survivors and a urine sample of a third survivor with Russian name by the DSTL, Porton Down, UK as well as urine samples of two other patients, evacuated by the German air ambulance to the Department of Clinical Toxicology of the Technical University of Munich (TU Munich), in which the Centers for Disease Control and Prevention (CDC), Atlanta, USA could verify Norcarfentanil and Remifentanil metabolites, there is evidence to suggest that the used aerosol in the theater at Moscow had consisted of a mixture of Carfentanil and Remifentanil. A fast loss of consciousness after inhalation of the aerosol and analgesia after awakening, as reported exemplarily by the first two mentioned patients, coincides with the effect of these fentanyl derivatives. These opioids are clinically used as injection narcotics—Carfentanil thereby possesses a 10,000-fold effectiveness of Morphine and is accredited only for use in animals—leading to anesthesia, analgesia and undesirable depression of breathing. Both substances have an only narrow therapeutic margin and Carfentanil could have been mixed with the smaller and shorter-acting Remifentanil to decrease the number of casualties that would have been resulted by a sole use of the former. The use of the indicated antidote Naloxon in this case could probably have saved a large number of lives if the nature of the used substances had been known or the clinical conditions of the casualties had been better recognized. Naloxon is a pure antagonist to all opioid receptors studied to date and is therefore able to antagonize all the effects of Morphine and further agonistic-acting substances [18]. The lives of the surviving 650 hostages were probably saved by the intervention of the Russian state as the terrorists were planning to explode the building.

5. Management of warfare agent attacks

Early decontamination is essential and should begin with the removal of the patient's clothing and thorough washing of the skin, while ensuring the responder is properly protected with specialized gear—such as butyl rubber gloves, gas masks, vinyl footwear and protective overgarments. Stabilization of vital functions and prompt evacuation from the hazardous area must also be prioritized. In cases involving nerve agents or vesicants, immediate skin decontamination is especially critical. It is only effective against vesicants when performed without delay and is vital for preventing skin absorption and systemic toxicity—particularly with low-volatility nerve agents like VX.

The first and most crucial step is the rapid removal of contaminated clothing. The effectiveness of decontamination diminishes over time, as chemical agents may permeate clothing, increasing the risk of cutaneous absorption under occlusive conditions. Skin decontamination methods fall into two categories: dry and wet. Dry decontamination involves the use of adsorbent powders such as fuller's earth, which remove liquid agents from the skin. However, care must be taken to prevent the generation of contaminated dust, which could pose an inhalation hazard.

Wet decontamination entails the use of large volumes of plain water, sometimes combined with surfactants such as soap or detergents to enhance solubility and removal of oily substances like VX.

The U.S. Food and Drug Administration (FDA) has endorsed the integration of decontamination and detoxification into a single step. Reactive skin decontamination lotion (RSDL), which contains 2,3-butanedione monoxime, polyethylene glycol and solvents, is specifically formulated to aid in the desorption of nerve agents from the skin and their subsequent breakdown via nucleophilic reaction. RSDL has demonstrated superior efficacy in treating percutaneous VX exposure compared to conventional decontamination agents such as fuller's earth. Overall, the first step in the effective treatment of nerve agent or vesicant poisoning must incorporate advanced and rapid decontamination and detoxification strategies [1, 19].

In cases where oral exposure is suspected in an unconscious patient, the administration of 50 g of medical charcoal via gastric tube should be considered, while ensuring that aspiration is avoided. Laxatives are generally unnecessary, as patients typically present with diarrhea [13].

5.1 Triage in mass casualty incidents involving toxic chemicals

In the aftermath of a chemical attack involving highly toxic substances and multiple casualties, establishing a triage protocol is essential. Given the likelihood of resource constraints, patients must be prioritized based on medical urgency:

- *First priority*: Patients in critical condition who can be stabilized if intensive care unit (ICU) resources are available.
- *Second priority*: Patients requiring immediate life-saving interventions within the next hour.
- *Third priority*: Patients with moderate injuries who can safely await delayed treatment or transport.
- *Fourth priority*: Patients in terminal condition who are unlikely to survive, even with antidote administration. These individuals should receive palliative care.
- *Fifth priority*: Patients at risk of delayed respiratory distress due to inhalation of pulmonary agents (choking agents). These individuals require observation for at least 24 hours following antidote administration.

5.2 Zoning and site management

At the scene, the incident commander must define the geographic extent of the affected zones. The *hot zone* (black area) represents the immediate contamination site and may extend up to 1 kilometer (km), depending on meteorological conditions, terrain and the volatility of the chemical agents involved. Surrounding this is the *warm zone* (gray area), where medical stabilization and decontamination procedures are performed to prevent secondary contamination. Beyond this lies the *cold zone* (white area), where the lead emergency physician coordinates patient triage and distribution to appropriate healthcare facilities [5].

6. Discussion

When preparing countermeasures against deliberate release of highly toxic compounds in public spaces, clinical toxicologists and poison centers, in particular, should play a complementary role, taking into account the responsibility of the designated emergency management authority and in cooperation with the PHS. In some emergency medical services, given the availability of a poison control center, there may also be toxicologically competent emergency physicians who can be called to the scene, if needed supported by a rescue helicopter to shorten transportation time and by the whole rescue system and whenever possible by the medical service of the armed forces. Diagnostic capacity, access to poison information by the worried well that place additional burdens on healthcare facilities and a sufficient supply of necessary antidotes and protective equipment for emergency responders and civilians on emergency management units are critical for a successful situation management.

In summary, these three elements—availability and access to specific diagnostic technology, therapeutic information for specialized staff in combination with an adequate stockpiling of antidotes and protective equipment—seem crucial for a preventive, public health-oriented preparedness for assaults with highly toxic substances in public spaces.

7. Materials and methods

A narrative review was compiled to present the actual level of knowledge in identification and handling of assaults with highly toxic chemical substances in public space. The experiences from incidents in recent years were given to colleagues in the field of public health at national congresses [5] who are supposed to have got a description of the theme's development as state of the art in presence, in how this understanding was reached and what may be expected from it prospectively.

The studied literature was collected by searching in www.pubmed.com using terms like GA, GB, GD, VX and references of found papers.

8. Conclusions

The recent use of nerve agents in military conflicts and assassination attempts has shown that the diagnosis and treatment of nerve agent exposure are an impending issue that has already made headlines at suitable occasions. The currently licensed oximes as antidotes have been in use for many decades, lacking the substantial improvement that still none of the available drugs can be used as a broad-spectrum oxime covering all relevant nerve agents and organophosphorus pesticides. Nevertheless, therapeutic gaps render further development crucial. The promising concept of a combination of different oximes with a complementary spectrum might be an interim solution to overcome current therapeutic limitations. A further cornerstone of nerve agent poisoning is the use of point-of-care diagnostics that render early diagnosis possible within 5 minutes by using a mobile ready-to-use kit to determine red blood cell AChE activity. Patients displaying inconclusive signs and symptoms might benefit from the therapeutic guidance these devices readily provide. Finally, the OP skin disclosure kit provides the opportunity to verify percutaneous exposure to low-volatility nerve agents, even before the first clinical signs occur [1, 19].

For the organization of concepts named under Discussion and their implementation, members of the PHS may assume a complementary role, for example as committed specialists in communal crisis teams and as communicators with health professionals, emergency services and the public. Confidence in reliable communication by actors of the state, an evidence-based approach and well-prepared, targeted purposeful measures, are essential, especially as comprehensive knowledge of the situation is still lacking. The present input wants to sensitize therefore and to deliver impulses for a review of existing preparedness. It does not claim a complete information about the complex issue, which probably underlies in parts also international confidentiality. Of special importance here is the additional coming into force of the "Chemical Weapons Convention (CWC) as Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on their Destruction" in 1997, which was compiled by the member states of the United Nations (UN) in 1992 and since then the OPCW has been founded and instructed to control the convention committed of 193 states [20].

For further reasons, succeeding generations of colleagues, at least in the Bavarian PHS, are already being familiarized with a potential public risk posed by chemical substances possibly through terrorist learning from the experiences of recent years. This was conducted through lectures or, during the severe adult respiratory syndrome coronavirus II (SARS-CoV-II) pandemic, through suitable scripts containing the main information on clinical symptomatology, toxicodynamics and therapy in cases of exposition to the most menacing, highly toxic chemical substances such as organophosphorus compounds like Sarin or vesicants like Sulfur Mustard gas. From 2018 onward, these lessons have been given to participants of the Bavarian Public Health training course who have additionally come from further southern German federal states like Baden-Württemberg, Rhineland-Palatinate, Saarland, Saxony or Thuringia. As a shortcoming, it cannot, of course, be ruled out that the topic may not receive the desired attention as there is not enough lecture time given to the subject during the complete course for PHS training. This paper therefore aims to raise awareness on this topic in its entirety and provide an impulse for a review of existing preparatory work [5].

Conflict of interest

The authors declare no conflict of interests.

Abbreviations

AChE	acetylcholinesterase
BChE	butyrylcholinesterase
DSTL	Defence Science and Technology Laboratory
EryAChE	erythrocyte acetylcholinesterase
GA	Tabun
GB	Sarin
GD	Soman
NHS	National Health Service
OPCW	Organisation for the Prohibition of Chemical Weapons
PHS	Public Health Service
PPE	personal protective equipment

QL	isopropyl aminoethylmethyl phosphonite
RVX	Russian VX
VG	2-(dimethylamino)ethyl N,N-dimethylphosphoramidofluoridate

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