CHAPTER 1

Treatment of Nerve Agent Poisoning

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1.1 Introduction

Therapy of nerve agent poisoning is a challenge for clinical toxicologists, specialists in intensive care units, medical doctors and all other medical personnel. The reason for this is manifold. Generally, nerve agents belong to a larger group of organophosphorus (OP) compounds whose single members present a high variability in physicochemical, toxicodynamic and toxicokinetic properties. Moreover, different types of absorption, *e.g.* inhalation, percutaneous exposure and oral ingestion, may affect the kinetics of poisoning dramatically. Hence, the onset of signs and symptoms may vary substantially and valuable time for an initial treatment may be lost if no adequate triggers to treat are available. Therapeutic approaches, therefore, may be complicated by simultaneously ongoing reactions within the body, *e.g.* aging, which frequently reduce the size of the therapeutic window in a dramatic way.

On the other hand, handling of victims itself may be a challenging problem, as secondary contamination may pose a life threatening risk for personnel

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and lead to contamination of medical facilities. This may also affect transport facilities, thereby preventing rapid transfer to the hospital.

Further uncertainties may arise from inadequate information about antidotal therapy as recommendations basing on a high level of evidence are not available. Thus, one has to rely on appropriate extrapolation from animal studies or poisoning with similar compounds, *e.g.* OP pesticides. Later, alternative therapeutic strategies used in intensive care units have been discussed and may be helpful for patient oriented treatment. All of these aspects will be discussed in the following chapter.

1.2 OP Compounds

1.2.1 General Remarks That Are Relevant for Therapy

The generic structure of OP compounds was first described by Schrader in 1937.[1,2] Among the huge variety of compounds, only some of them were identified as potentially useful military nerve agents. Today, they are listed in the Annex on Chemicals, Schedule 1 of the Chemical Weapons Convention (http://www.opcw.org/chemical-weapons-convention/). The G-series agents include GA (tabun), GB (sarin), GD (soman) and GF (cyclosarin). The V-series agents (VX, CVX and RVX) were developed after World War II. All of them are chiral compounds with at least one (two in the case of soman) optically active centers. The isomers of nerve agents show marked differences regarding their stability in biological systems and their human toxicity. Due to big differences in their chemical structures nerve agents differ widely in their physiochemical properties (for a comparison see Volume 1, Chapter 3). All nerve agents are liquids at room temperature with boiling points higher than water. Their different volatility and vapor pressure lead to their classification into volatile (G-series) and non-volatile (V-series) nerve agents.[3–5] Nevertheless, modification of a single substance is possible, *e.g.* thickened soman is persistent while aerosolized VX can pose a very serious inhalational threat. Thereby, the physicochemical properties are determinative for military use and for exposure scenarios. Sarin for example will persist in soil in convenient climates (sunshine, slight wind, 15 °C) for several hours only, while V-agents may persist for a longer period in the soil, *e.g.* at cold temperature (−10 °C) and dry climates for up to 4 months.[6]

The military intention to find OP compounds with enhanced human toxicity was in contrast to the civilian attempt to reduce human toxicity of highly effective OP pesticides. OP compounds are used increasingly as pest-control agents in the agricultural industry, especially in the developing world. Today, OP pesticides that are highly toxic to humans are widely banned in developed countries, but a high variety of OP pesticides are still available and causing human OP poisoning, especially in third world countries. Mainly in the context of suicide attempts, OP pesticides account for about 3 million intoxications per year, leading to death in up to 260 000 cases.[7,8] A high number of studies on pesticide poisoning are available. However, differences between

compounds regarding toxicity, physicochemical properties, reactions with target enzymes and metabolism affect the clinical course. In addition, different exposure scenarios, *e.g.* most frequently suicidal attempts involving ingestion of multiple lethal dose, 50% (LD_{50})'s, result in mega-dose poisoning. Hence, findings from OP pesticide poisoning need careful assessment before being translated to nerve agent poisoning.

1.2.2 Toxicology of OP Compounds

1.2.2.1 Toxicokinetic Aspects Relevant for Therapy

Exposure to OP compounds may be by ingestion, percutaneous absorption, inhalation or injection. In military or terrorist scenarios, exposure to vapor, aerosol or droplets of nerve agents appear relevant. Thus, exposure may either occur after inhalational or percutaneous absorption. As details on the toxicokinetics are discussed in Volume 1, Chapter 3 and 8, only a few aspects directly relevant for therapy are mentioned here. For further information please also refer to John *et al.*[9]

First, absorption through mucous membranes and distribution of volatile G-type nerve agents, *e.g.* tabun, sarin and soman, is expected to be very fast, thus leading to a very rapid onset of cholinergic crisis. Hence, treatment has to be started immediately, at best at the time of exposure. To address this special requirement during the Cold War, military forces equipped their personnel with autoinjectors for self and buddy aid that were to be applied as soon as a soldier suffered from the first signs and symptoms of cholinergic crisis. This strategy, nowadays, has to be expanded to scenarios of unexpected use of nerve agents in asymmetric military conflicts and terrorist attacks. In such scenarios, the majority of victims reaching medical facilities[10] are expected to be exposed to doses of less than 5 LD_{50}'s of the respective agent. Accordingly, the rapid binding and hydrolysis of G-agents by endogenous mechanisms will result in a comparatively short residence time in the systemic circulation. In conclusion, very early administration of effective antidotes is important and lifesaving. Long term therapy will only be necessary in severely poisoned victims or in patients developing complications as a result of an initial cholinergic crisis.

In contrast, after percutaneous exposure as typically expected in V-agent poisoning, toxic blood levels will develop more slowly. Development of a subcutaneous depot has been hypothesized from which the agent may be distributed to other compartments for a prolonged time. Initially, ongoing absorption of the agent results in distribution in the systemic circulation and binding to various proteins. This is reflected by a slow decrease of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE) activities, and delayed agent transfer into tissues. As a consequence, systemic signs of poisoning become obvious after a time lag, which may be several hours. Hence, early diagnosis of exposure is essential to initiate antidote therapy prior to onset of life threatening signs (see Chapter 5). Toxic agent concentrations may persist

for hours or even days and require intensive treatment for several days. In these patients, careful therapeutic monitoring is of greatest importance in order to avoid too early discontinuation of antidotal administration.

1.2.2.2 Toxicodynamics of Nerve Agents

1.2.2.2.1 Reactions of Nerve Agents with AChE. OP compounds, *i.e.* nerve agents and pesticides, inhibit serine esterases such as AChE (E.C. 3.1.1.7), BChE (E.C. 3.1.1.8), carboxylesterases and neuropathy target esterase (NTE; E.C. 3.1.1.5) by covalently binding to a serine residue of the enzyme's catalytic center. Inhibition of AChE is regarded as the main mechanism for nerve agent toxicity. The velocity of AChE inhibition is dependent on the chemical properties of the individual nerve agent and can be described by the second order inhibition rate constant (k_i; Table 1.1). AChE–OP compound conjugates determine further compound specific reactions that affect toxicity and therapeutic options (Chapter 5, Figure 5.2). The first reaction, spontaneous hydrolysis, often denoted as spontaneous reactivation, appears of minor importance for nerve agents, but may contribute to several specific features in OP pesticide poisoning. The second, a dealkylation reaction, denoted as aging, results in a stable complex, which can no longer be reactivated by nucleophiles under physiological conditions. From a therapeutic point of view, the aging velocity is decisive for the therapeutic window in which OP residues can be cleaved from the inhibited AChE by nucleophiles. AChE is located in synapses in close vicinity to receptors in the central and peripheral nervous system (nicotine and muscarine receptors), sympathetic and parasympathetic ganglia (nicotine receptors), and parasympathetic nerve endings

Table 1.1 Inhibition rate constants of OP compounds derived from erythrocyte AChE from humans and various animal species.[a]

	Inhibition rate constant k_i (10^6 M^{-1} min^{-1})			
	Guinea pig	Swine	Cynomolgus monkey	Human
G-agents				
Cyclosarin	160	268	735	439
Soman	45.9	75.8	250	193
Sarin	12.9	16.6	40.7	39.8
Tabun	3.8	5.0	12.0	18.2
V-agents				
VR	159	188	396	458
VX	81.7	44.3	119	115
OP pesticides				
Paraoxon-methyl	0.19	0.84	0.53	1.1
Paraoxon-ethyl	0.45	1.1	4.6	3.3

[a]Data from Worek and Thiermann.[13]

(muscarine receptors), neuromuscular junctions (nicotine receptors), as well as on membranes of red blood cells. AChE hydrolyzes acetylcholine (ACh), which mediates chemical synaptic transmission at cholinergic synapses. AChE is one of the most effective enzymes known, hydrolyzing approximately 10 000 ACh molecules per second. Inhibition of this decisive enzyme results in disturbance of neurochemical transmission, thereby initiating the clinical picture of cholinergic crisis (see below). For assessment of the toxicological effects of OPs as well as the therapeutic effectiveness of antidotes it has to be considered that AChE is encoded by a single gene,[11] resulting in the same functional structure of its active center in all tissues.[12] However, there are species differences in AChE structure, which, in part, lead to markedly different kinetic properties. This finding needs adequate appreciation when assessing new therapeutic approaches as most of the results are derived from animal experiments.

These differences also impact therapeutic measures and will be mentioned later again when discussing effective plasma concentrations of oximes.

1.2.2.2.2 Binding of Nerve Agents to Other Targets. As highly reactive compounds, nerve agents are able to interact with a variety of proteins in the body. Such binding reactions affect the toxicity of nerve agents as binding may reduce the amount of free nerve agent (*e.g.* binding to BChE and carboxylesterases) and chemical modifications of other proteins may induce pathophysiological effects (*e.g.* binding to AChE and NTE). The inhibitory potency of nerve agents towards AChE and BChE is in the same order of magnitude.[14] Therefore, BChE may scavenge nerve agents in the systemic circulation, thereby preventing or delaying distribution to cholinergic synapses. Indeed, this effect is the subject of research efforts directed towards producing human BChE in various expression systems in larger quantities. Unfortunately, BChE is inhibited by nerve agents and can only react stoichiometrically. Hence, large amounts of this bioscavenger need to be administered to achieve a therapeutic effect.[14] Accordingly, this therapeutic approach appears only rational for treatment of poisoning with highly toxic nerve agents, but will have only a marginal effect in poisoning with OP pesticides, which show lower toxicity and much higher plasma levels. In a similar way, although there are comparably high amounts of albumin present in the plasma, due to the low affinity, scavenging of nerve agents by this protein does not substantially contribute to an antidotal effect. At best, in severe poisoning, nerve agent adducts at albumin residues can be used for biomedical verification.[9] Similarly, chemical modifications of other proteins and enzymes generally require higher concentrations than expected in nerve agent poisoning for substantial interactions.[9] On the other hand, research is directed towards enhancing the hydrolytic activity of human (*e.g.* paraoxonase[15]) or bacterial (*e.g.* phosphotriesterase[16]) enzymes in order to develop catalytic bioscavengers (see Chapter 2). A further approach consists of the development of small molecule scavengers that are able to bind to or

hydrolyze nerve agents.[17] These approaches are far from clinical use at present and are therefore not discussed here in detail.

1.3 Protective Measures and Decontamination

As outlined in Volume 1 Chapter 3 (see also Table 3.4), nerve agents are characterized by high human toxicity (Table 1.2).

Due to this high toxicity, the general population and accordingly medical personnel are at risk when exposed to low concentrations of nerve agents. An estimate of toxic levels that are relevant for medical personnel can be derived from the Acute Exposure Guideline Levels (AEGLs) developed by the US Environmental Protection Agency (USEPA) (Table 1.3). These values represent threshold exposure limits for the general public and are applicable to various emergency scenarios. These threshold values allow protection of the general public, including sensitive sub-populations (*e.g.* infants and children), but not hypersensitive or hyper-susceptible individuals.

The high toxicity of nerve agents, reflected by the AEGL values, emphasizes the need for effective protection of first responders and medical personnel. In view of the difficulty in detecting such low levels of agent, an anticipated dissemination of nerve agents calls for full protective gear. Especially for rescue operations in highly contaminated areas and activities in wet environments, butyl rubber suits are recommended. For other activities, semi-permeable suits are considered adequate and have the advantage of lower physical burden but provide limited protection against aerosols. Full protective gear is needed for as long as the absence of nerve agents is not verified.

Protective gear can impair the handling of patients, making procedures such as oro-tracheal intubation and venous puncture very difficult, and requires additional training.[19,20]

Not only medical personnel performing pre-hospital treatment must be protected. It is of decisive importance to protect medical facilities, including hospital personnel and other patients. It was one of the most important lessons learned from the Tokyo sarin attack that toxicologically relevant nerve agent concentrations may arise when patients exposed to even comparably low doses enter medical facilities without being adequately decontaminated.[21]

Table 1.2 Human lethality of nerve agents after percutaneous and inhalation exposure.

	LD_{50}			
	Sarin	Soman	Tabun	VX
Percutaneous[b] (μg kg^{-1})	$24–28 \times 10^3$	18×10^3 (LD_{low})[a]	$14–21 \times 10^3$	86 (LD_{low})[a]
Inhalation[c] mg $min\ m^{-3}$ (vapor)	100	50	400	10

[a]LD_{low}: minimal amount of a chemical that has been shown to be lethal.
[b]Data from John *et al.*[9]
[c]Data from Sidell.[18]

Table 1.3 Acute exposure guideline levels of nerve agents.[a,b]

	10 min	0.5 h	4 h
	AEGL-1 (mg m^{-3})		
Tabun	0.0069	0.0040	0.0014
Sarin	0.0069	0.0040	0.0014
Soman/GF	0.0035	0.0020	0.0007
VX	0.00057	0.00033	0.00010
	AEGL-2 (mg m^{-3})		
Tabun	0.087	0.050	0.017
Sarin	0.087	0.050	0.017
Soman/GF	0.044	0.025	0.0085
VX	0.0072	0.0042	0.0015
	AEGL-3 (mg m^{-3})		
Tabun	0.76	0.38	0.14
Sarin	0.38	0.19	0.070
Soman/GF	0.38	0.19	0.070
VX	0.029	0.015	0.0052

[a]Three AEGLs have been defined as follows: "AEGL-1 gives the airborne concentration of a nerve agent above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects. However, the effects are not disabling, transient and reversible upon cessation of exposure. AEGL-2 gives the airborne concentration of a nerve agent above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape. AEGL-3 gives the airborne concentration of a nerve agent above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death".

[b]Data from the US Environmental Protection Agency http://www.epa.gov./oppt/aegl/pubs/results31.htm; search performed July 2015.

Decontamination itself is defined as reduction or removal of chemical agents by physical means or by chemical neutralization or detoxification. Decontamination efficacy is time dependent and at least provisional decontamination should be performed immediately after contamination.[22] In most cases, one will not know if and at which part of the body a nerve agent contamination occurred, making undressing and whole body decontamination mandatory for effective removal of agents from the body surface.

Generally, liquid and contaminated soil/dust have to be removed by any means as fast as possible. Percutaneous absorption is dependent on the barrier qualities of the stratum corneum, which is determined by factors including location on the body, thickness, and the presence and number of hair follicles.[23] Hair follicles in particular appear critical for nerve agents to bypass the corneal barrier.[23]

Various decontamination products are available on the market. Corrosive decontaminants, *e.g.* sodium hypochlorite (bleach), are highly effective but due to their irritating and damaging effects on skin are not recommended for skin decontamination.

At present, Reactive Skin Decontamination Lotion (RSDL) appears to be an appropriate decontaminant for humans in order to perform spot

decontamination. RSDL was introduced in several military forces as a skin decontamination product to remove or neutralize chemical warfare agents, T-2 toxin and many pesticide related chemicals from the skin. It received a license from the US Food and Drug Administration (FDA) and has received a European CE Mark and an Australian TGA license (http://www.rsdl.com/skin-decontamination/rsdl/). However, RSDL is not approved for use in the eyes or in wounds, as it may impair wound healing.[23]

In conclusion, a decontaminant for skin, eye, wound and mucous membrane decontamination is not available at present.

If eyes are suspected to be contaminated, extensive rinsing should be performed with, ideally, physiological solutions, *e.g.* 0.9% saline solution, but sterile or at least clean water could be used. However, care should be taken in order to prevent eye damage due to vigorous procedures.

Equally, wounds should be extensively rinsed with sterile physiological solutions. Here, however, a thorough balance may be necessary in order to prevent secondary damage due to exposure to great amounts of fluid in large wounds.

In conclusion, effective personnel decontamination combines an immediate spot decontamination, *e.g.* by RSDL, followed by undressing and whole body decontamination by showering with plenty of water or soapy water at ambient temperature.

1.4 Clinical Picture of Nerve Agent Poisoning

1.4.1 Acute Nerve Agent Poisoning

The failure of inhibited AChE to hydrolyze the neurotransmitter ACh results in endogenous ACh flooding followed by over-stimulation of muscarinic and nicotinic ACh receptors. In general, the severity of signs of poisoning is dependent on the level of synaptic AChE inhibition. The localization of muscarinic and nicotinic synapses in the nervous system allows the differentiation between nicotinic and muscarinic mediated symptoms of OP poisoning.[24]

1.4.1.1 Central Nervous System

Central manifestations of ACh accumulation are mediated by nicotinic and muscarinic receptor over-stimulation and result in headache, confusion, ataxia, tremor, psychosis, convulsions, coma and central respiratory depression.

1.4.1.2 Autonomic Nervous System

1.4.1.2.1 Sympathetic Nervous System. Nicotinic ACh receptors are located at paravertebral sympathetic ganglions. In response to the preganglionic stimulus, postganglionic neurons release noradrenaline, which activates adrenergic receptors on the peripheral target tissues. Accordingly, overstimulation of

ACh receptors of the sympathetic nervous system induces a short lasting initial adrenergic/noradrenergic stimulation, which leads to secretion of adrenaline from the adrenal medulla and may cause transient tachycardia and increased blood pressure in the initial stage of poisoning.[25] In this phase, a systemic administration of atropine may aggravate tachycardia.

1.4.1.2.2 Parasympathetic Nervous System. ACh is the primary neurotransmitter of the parasympathetic nervous system and neurotransmission occurs in two stages: when stimulated, the preganglionic neuron releases ACh into the synaptic cleft, which acts on nicotinic receptors of postganglionic neurons; the postganglionic neuron then releases ACh to stimulate the muscarinic receptors at the target organs. The axons of presynaptic parasympathetic neurons are usually long and the ganglions located in or near their target organ. Muscarinic effects of OP poisoning occur at cholinergic end-organs resulting in vagal over-stimulation and cholinergic crisis with hypersecretion of secretory glands (rhinorrhea and bronchorrhea), smooth muscle contraction (bronchoconstriction, miosis and abdominal cramps) and, subsequent to the initial stage of poisoning, effects on the cardiovascular system (hypotension, bradycardia and arrhythmia). Hence, the parasympathetic nervous system overrides sympathetic effects and dominates during the typical cholinergic crisis.[25]

1.4.1.3 Somatic Nervous System

Nicotinic ACh receptors are located at muscle endplates of skeletal muscles. Consequences of AChE inhibition at neuromuscular junctions are muscle fasciculations and hyperreflexia followed by muscle weakness and depolarization block with reduced tendinous reflexes. Paralysis of the respiratory muscles finally may result in death.

1.4.1.4 Conclusion

The development of signs and symptoms of nerve agent poisoning varies depending on the dose and the route of exposure of the nerve agent. Local signs and symptoms (*e.g.* miosis after vapor exposure to the eyes or fasciculations at the exposure site after liquid exposure) may precede systemic effects (Chapter 5, Figure 5.3).

Different receptor systems are involved in the development of cholinergic crisis. The cause of death in the acute phase of nerve agent poisoning is respiratory dysfunction due to a combination of effects on respiration:

- Muscarinic induced bronchorrhea and bronchoconstriction (muscarine receptors)
- Impaired respiratory central drive (muscarine and nicotine receptors)
- Nicotinic mediated progressive respiratory muscle paralysis (nicotine receptors)

1.4.2 Intermediate Syndrome

Wadia *et al.*[26] reported on neurological manifestations in OP insecticide poisoning. The group described a phenomenon arising later, during atropine therapy, characterized by proximal limb weakness, areflexia and cranial nerve paralysis.[26] Later, in 1987, Senanayake and Karalliedde[27] defined an intermediate syndrome occurring in about 20% of patients poisoned by OP pesticides.[28] This syndrome typically develops 2–4 days after exposure when the signs of acute cholinergic syndrome are no longer obvious. It is characterized by weakness of respiration (diaphragm, intercostal muscles and accessory muscles including neck muscles) and proximal limb muscles. Such a syndrome has not yet been reported in cases of nerve agent poisoning.[29] However, in 1981, Weger and Szinicz[30] found in dogs, 3 weeks after having recovered from soman poisoning, a weakness of neck muscles making them unable to lift their heads. This feature was accompanied by a decrease in cholinesterase activity. Hence, there are no conclusive data ruling out the development of an intermediate syndrome in nerve agent poisoning. One should be cautious in order to avoid overlooking such a life threatening complication.

1.4.3 Organophosphate Induced Delayed Neuropathy

Organophosphate induced delayed neuropathy (OPIDN) is characterized by a symmetrical sensorimotor axonopathy that tends to be most severe in long axons. It usually causes weakness of peripheral muscles in the hands and feet with a variable sensory impairment that generally occurs 7–14 days after exposure to several OP compounds.[29,31,32] OPIDN is initiated by a sufficiently strong and extensive inhibition of the NTE. It appears that even aging of the inhibited NTE is necessary to induce OPIDN.[32] However, much higher nerve agent concentrations are necessary to inhibit NTE than those occurring during nerve agent poisoning in humans. Thus it appears unlikely that nerve agents possess the capability to cause OPIDN in survivors of poisoning.[29]

1.5 Pretreatment

One knows that poisoning by several nerve agents, *e.g.* soman and tabun, cannot be treated sufficiently with atropine and oximes. To enable survival of soldiers during an attack with these agents, the concept of medical prophylaxis was developed and belongs to the NATO doctrine.[33] This approach is based on early animal experiments[34,35] showing that administration of a carbamate prior to the nerve agent analog DFP resulted in convincing protection rates.[36] Finally, this finding was translated to human use and pyridostigmine bromide was approved by the FDA on 5th February 2003 for prophylaxis against the nerve agent soman (http://www.fda.gov/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/ucm130342.htm). This concept aims to carbamylate synaptic AChE partially, thus preventing

phosphylation by a nerve agent. After clearance of unbound nerve agent from the body, decarbamylation of AChE is expected to result in a small fraction of active AChE in the synaptic cleft, resulting in improved survival. It was estimated that carbamylation of 20–40% of AChE should be sufficient for a relevant protective effect. To this end, a daily oral dose of 3 × 30 mg pyridostigmine is required prior to nerve agent exposure.[33] Although a variety of side effects may occur under such treatment, fewer than 1% of the US troops had to discontinue pyridostigmine administration during the Gulf War Conflict.[22] Meanwhile, it was shown experimentally that after pyridostigmine prophylaxis, soman may not lead to a complete inhibition of AChE. It appears that a very small portion of AChE remains active under such conditions,[37] which might be decisive for survival. It is notable that the pretreatment approach only has relevance for military personnel and a few selected first responders.

1.6 Differences Between Nerve Agent and OP Compound Pesticide Poisoning

The acute toxicity of nerve agents and OP pesticides is induced by inhibition of AChE. Nevertheless, there are several decisive differences between nerve agent and pesticide poisoning that have to be considered when translating research results on the therapeutic effectiveness of oximes. Generally, only a few compounds fulfilled the requirements to be developed as nerve agents. Principally, they were selected as chemical warfare agents because of their higher toxicity towards humans. This is reflected by the low lethal doses, which are a result of their high inhibitory potency (the k_i of nerve agents is in the range of 10^{-7} to 10^{-8} *versus* 10^{-3} to 10^{-6} for pesticides). Accordingly, the toxic concentration of a nerve agent in the body is generally lower compared with pesticides. In addition, inhalation and percutaneous exposure are most likely with nerve agents while severe pesticide poisonings occur after suicide attempts with oral uptake of large doses. This leads to resorption of huge amounts of the poison, and results in high and persistent concentrations in the body. Moreover, in order to optimize the efficacy of pesticides, commercial products contain different solvents and stabilizers. These ingredients may induce additional toxic effects and may aggravate the toxicity of neat agents. As an example, a study by Eddleston *et al.* may be mentioned,[38] in which a possible contribution of solvents to the toxicity of dimethoate in minipigs was shown.

The aforementioned factors may effect therapeutic strategies and appear to influence dramatically the assessment of oxime effectiveness. Generally, in most clinical reports, cohorts of patients were formed who were poisoned by different pesticides. Although data on severity of intoxication are mostly presented, clear stratification is hampered due to different and often unknown pesticide doses, different times to first treatment and access to hospital care, and different strategies of treatment, *etc.* Moreover, most studies included only small numbers of patient, which almost prevents the formation of

sub-groups with comparable parameters. Thus, it is no surprise that oxime effectiveness (see below) in OP pesticide poisoning is still a matter of debate. It is a challenge to extract the relevant results from current pesticide research and translate them to nerve agent poisoning.

A further important aspect is the number of poisonings. In general, single patients poisoned by OP pesticides need treatment, while the homicidal use of nerve agents may result in a mass casualty scenario. Accordingly, individual patient care in well equipped intensive care units cannot be expected in nerve agent exposure scenarios. Triage, artificial ventilation and drug administration are the major tasks to ensure survival of the maximum number of patients. The capacity for artificial ventilation will for sure be the limiting factor and requires the availability and early administration of effective antidotes to restore the respiratory drive, to reduce bronchoconstriction and bronchorrhea and to improve respiratory muscle function.

1.7 Therapeutic Regimen of Nerve Agent Poisoning

1.7.1 General Considerations

Signs of nerve agent induced cholinergic crisis are characteristic. They may develop rapidly, especially after inhalational exposure and may frequently lead to comatose and seizing patients with severe respiratory distress resulting in death within minutes.[10,18] Hence, even the suspicion of OP poisoning necessitates the immediate start of antidotal treatment. Aside from clinical signs, ongoing inhibition of AChE, especially from percutaneous nerve agent exposure, may be an appropriate trigger to treat (see Chapter 5) in cases with delayed onset. In general, the identity of the nerve agent will be unknown initially, requiring a standardized emergency therapy to counteract the cholinergic crisis. Individualized therapy based on the nerve agent and severity of poisoning may follow later on. The standard post exposure antidotal treatment of OP poisoning includes a muscarinic receptor antagonist, usually atropine, an oxime as a reactivator of OP inhibited AChE, usually pralidoxime or obidoxime, and an anticonvulsant, usually diazepam, in combination with further symptomatic treatment, *e.g.* artificial ventilation.

1.7.2 Atropine

Atropine represents the cornerstone in antidotal treatment of OP poisoning. Adequate administration facilitates effective suppression of life threatening muscarinic symptoms.

Atropine (racemic D-hyoscyamine/L-hyoscyamine) belongs to the family of tropane alkaloids that are biosynthesized in flowering plants of the Solanaceae family, *e.g. Atropa belladonna* (deadly nightshade), *Datura stramonium* (thorn apple) and *Hyoscyamus niger* (henbane).[39] Its pharmacological action results from competitive antagonism of ACh at muscarinic (M1–M5) receptors. Although atropine lacks selectivity for muscarinic receptors, there is a

hierarchy of relative sensitivity, which is most probably determined by the degree of parasympathetic tuning of the single end organs as well as the contribution of intramural neurons and reflexes.[40] At low doses, salivary and bronchial secretion and sweating are depressed. Larger doses result in dilatation of pupils, inhibition of the lens to near vision and blocking of vagal effects on the heart leading to an increased heart rate. A further increase in dose results in inhibition of micturition and decrease of gut tone and motility.[40] Still higher dosing leads to inhibition of gastric motility and particular secretion.[40] A certain consideration of atropine's effects on the central nervous system is necessary. At doses used in clinical routine (0.5–1 mg), only mild vagal excitation due to stimulation of the medulla and higher cerebral centers is expected in adults. Higher doses, however, are associated with more prominent central nervous system effects, finally resulting, at the highest concentrations, in depression associated with circulatory collapse and respiratory failure.

Accordingly, atropine poisoned patients present with peripheral and central signs of poisoning that allow clinical diagnosis.[25] The peripheral anticholinergic syndrome is dominated by tachycardia, inability to sweat and dry mucosa. Frequently, the head is red, gastrointestinal tone is reduced with disturbances of defecation. Most striking is a nearly complete lack of sweat at the armpits and the typical mydriasis accompanied by loss of accommodation. Initially, patients may present tired with somnolence. This behavior will turn to agitation, restlessness, irritability, disorientation (time, location) and hallucination (optical) or delirium.[25] These symptoms may be followed by possibly repetitive epileptic seizures and deep coma. Spontaneous muscle twitching and choreoathetoid movements can be observed, occasionally. Children are more sensitive than adults and especially vulnerable for epileptic seizures accompanied by hypoxic residuals.[25]

Hence, atropine therapy requires a balance between beneficial and adverse effects. As the antidotal mechanism is based on competition, the atropine dose has to be carefully adjusted to clinical sings, thereby avoiding adverse side effects.

1.7.2.1 Self and Buddy Aid

Due to the threat of an attack with nerve agents during the Cold War, soldiers were equipped with atropine to be administered *via* autoinjectors for self and buddy aid. It was agreed that autoinjectors would be filled with 2 mg atropine sulfate, a dose that is still regarded as standard today. This decision was based on the finding that 2 mg appeared to be reasonably effective while higher doses are expected to produce embarrassing effects on troops with operational responsibilities.[18] At the dose of 2 mg, an increase in heart rate of about 35 beats per min, dry mouth, dry skin, mydriasis and disturbance of accommodation may be expected. These effects might last for 4–6 h with the exception of blurred vision, which may persist for about 24 h.[18] In particular, the signs of reduced sweating need careful consideration, as this may contribute substantially to disability during exhausting tasks on a

military mission or during a complex mass casualty scenario. The administration of three autoinjectors (6 mg) may result in mild mental disorder (*e.g.* drowsiness or forgetfulness), together with other peripheral signs of poisoning, when administered in the absence of nerve agent poisoning.[18] Accordingly, many armed forces are equipped with autoinjectors containing about 2 mg of atropine sulfate. It depends on national doctrine whether the autoinjectors contain atropine alone, *e.g.* AtroPen, 2.0 mg atropine sulfate, or whether they are additionally filled with an oxime, *e.g.* pralidoxime [antidote treatment-nerve agent autoinjector (ATNAA), containing 600 mg pralidoxime and 2.1 mg atropine] or obidoxime (ATOX II, containing 220 mg obidoxime and 2 mg atropine sulfate), and also depends on how many autoinjectors are planned to be distributed to each soldier. In many countries, three autoinjectors containing a total of 6 mg atropine sulfate, frequently together with an oxime, are used. In general, it is recommended to use the first autoinjector when the initial signs appear. After 5–10 min, the second autoinjector should be administered if no improvement occurs, followed by the third after a further 5–10 min in the case of no improvement. In severe cases, all three autoinjectors should be administered at the same time. This medical strategy, however, presupposes training of the soldiers in handling of autoinjectors, awareness of the signs of poisoning and distribution of autoinjectors to the soldiers. In many countries, this distribution is dependent on an assessment of the military situation and, therefore, needs an adequate nerve agent threat level for delivery in time. In the civilian environment, autoinjectors will not be of relevance for self and buddy aid.

1.7.2.2 Treatment by Medical Specialists

In a mass casualty scenario with a nerve agent, a huge number of patients may arrive simultaneously in conditions that may be described as "poor", "moderate" or "mild", as well as patients who think that they have been poisoned but have not (worried well).[10] Thus, dosing of atropine needs adequate assessment and the first challenge would be to differentiate the worried well, to whom no atropine should be administered.

One lesson learned from the Tokyo sarin attack, when people were exposed to nerve agent vapor, is that most patients are expected to suffer from miosis and headache (about 99 and 83%[41]). Further eye effects may be eye pain, blurred vision, dim vision, conjunctival injection and tearing.[41] As the eye is a first path of entry and directly exposed to nerve agent vapors in unprotected individuals, these effects may be induced locally without prior distribution in the body. The headache mentioned above may also be in part related directly to the local spasm of eye muscles. In such cases, local application of atropine or homatropine should be considered.[18]

Independent from the route of exposure, systemic signs have to be treated systemically with atropine. The lessons learned from the Iran–Iraq war[10] and the Tokyo sarin attack[41] show that the velocity of adequate atropinization is

decisive. This is underlined by studies on OP pesticide poisoning showing a clear benefit from rapid atropinization (for a review see ref. 42 and 43). At present, the regimen suggested by Eddleston and colleagues[44] appears appropriate. It consists of starting with 2 mg followed by an assessment after 5–10 min and consecutive doubling of the dose (4–8 to 16–32 mg) if there is no clinical improvement. The criteria for adequate atropinization could be (i) clear lung on auscultation, (ii) heart rate >80 beats per min, systolic blood pressure >80 mmHg, (iii) dry axilla, and (iv) pupils no longer pinpoint.[44] As there is an ongoing discussion on the appropriate dose, an alternative concept, basing on experiences from Iran, is presented. In this concept, it is suggested to start with 2 mg in mild, 2–10 mg in moderate and 10 mg in severe cases, maintaining a status of mild to moderate atropinization until the patient becomes asymptomatic.[45,46]

One important aspect when suggesting fast atropinization needs to be considered. In several textbooks, it is stated that hypoxic patients may be at risk of developing ventricular tachycardia or fibrillations when treated with atropine and, thus, atropine should be avoided if possible before resuscitation with oxygen or artificial ventilation.[47] In a recent review, however, it was convincingly shown that atropine induced life threatening dysrhythmias in OP pesticide poisoned patients are rather unlikely.[48]

In conclusion, fast and adequate atropinization is key for survival and should be initiated as soon as possible. In situations in which intramuscular (i.m.) or intravenous (i.v.) administration is not possible intraosseous administration should be considered.

After reaching adequate atropine levels, atropine should be administered *via* an i.v. line in severe cases. Experiences from patients with pesticide poisoning allow the conclusion that in the post acute phase, a dose of 0.5–1 mg h^{-1} should be sufficient,[25] although the dose should be adjusted to clinical conditions. Generally, however, it appears that patients with severe nerve agent poisoning tend to require lower doses of atropine than patients with severe OP pesticide poisoning.[46] In any case, the criteria mentioned above can be used even later on during a stay at the intensive care unit or a field hospital to ensure adequate atropinization. However, it should be considered that, especially during a later stage of cholinergic crisis, "over-atropinization" should be avoided. Foroutan[10] found that several patients may develop a "atropine immunization", resulting in the requirement of higher dosages of atropine each day; these patients occasionally went on to die.[10] A similar observation was also seen in OP pesticide poisoning treated in the toxicological intensive care unit in Munich in the 1980s and 1990s. Here, after stopping atropine, it appeared that patients re-developed cholinergic sings and even needed higher atropine doses for antagonism. As there was uncertainty, these high doses were not stopped until BChE activity increased substantially (personal communication, Prof. Zilker). Such high dosing most probably would not have been necessary if atropine weaning had been performed more resolutely.

However, atropine is not suitable to counteract symptoms mediated by overstimulation of nicotinic ACh receptors. Hence, nicotinic signs of OP poisoning are treated by restoration of AChE function by oximes. Thereby, the efficacy of oximes to reactivate OP inhibited AChE depends on the structure of the inhibiting agent and the oxime. As oxime and atropine are less effective to counteract convulsions, an anticonvulsant complements the pharmacological antidotal management of OP poisoning.

1.7.3 Oximes

1.7.3.1 General Background

As early as 1955, researchers in the USA[49] and UK[50] published independently that the pyridinium compound pralidoxime (*i.e.* 2-PAM iodide) efficiently reactivated phosphorylated cholinesterases. Only 3 years later, Namba and Hiraki came to the conclusion "Hithertoo, alkylphosphates poisoning has been treated mainly by atropine, but now atropine is replaced by pralidoxime".[51] Research programs on oximes were started in the 1950s and are still going on. Initially, the focus was on the identification of an oxime that is effective against soman. For more than two decades the main focus has been on the development of broad spectrum oximes covering the range of structurally different nerve agents. Unfortunately, no such compound has been identified so far.[52,53] At present, only pralidoxime, obidoxime, TMB-4 and HI-6 are in clinical use. Pralidoxime is most extensively used (*e.g.* in the USA, UK and Asian states) while obidoxime is in use in several European countries (*e.g.* Germany and The Netherlands).[54] TMB-4 is only used in autoinjectors in Israel.[55] HI-6 has already been tested in a few selected OP pesticide poisoned patients[56] and is stockpiled in autoinjectors by a few nations (*e.g.* Canada and Sweden). Unfortunately, HI-6 is not commercially available at present. Several programs are running in order to develop HI-6 as a licensed drug. It should be mentioned that pralidoxime and obidoxime are licensed in several countries (*e.g.* pralidoxime by the FDA in the USA and obidoxime by the BfArM in Germany) for civilian use. The huge number of other oximes developed during the last few decades are far away from clinical use and are therefore not considered in this chapter.

Oximes are pyridinium compounds that break the covalent bond between OP compounds and AChE by nucleophilic attack, thus restoring enzyme function to OP inhibited AChE (for review see ref. 57 and 58). This reaction takes place at the active center at the bottom of an approximately 20 Å deep and 4 Å wide gorge[59,60] that is lined with aromatic amino acids[61] that interact with inhibitors and reactivators. These spatial constraints and the structure of the most bulky oximes do not provide optimal geometry for fast reactivation.[57] Thus, until now, a clear structure–activity relationship could not be established for oximes and individual OP compounds.[52,62–64] Moreover, as mentioned above, there are remarkable species differences in susceptibility to inhibition, spontaneous reactivation and aging that also affect reactivation substantially.[65–68]

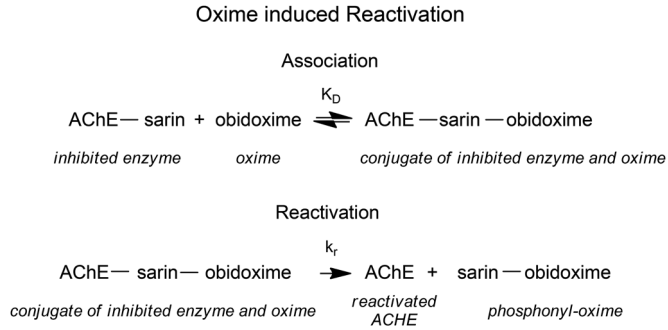

Figure 1.1 Reactivation process of inhibited AChE by oximes, exemplified by the nerve agent sarin and obidoxime.

The oxime induced reactivation consists of two steps (Figure 1.1).[57,69] First, there is a bimolecular reaction of the inhibited enzyme, *e.g.* sarin inhibited AChE, with an oxime, *e.g.* obidoxime, resulting in a conjugate of the inhibited enzyme and the oxime. The velocity of this reaction depends on the concentration of both reactants. As the concentration of AChE in the body is constant, an increase in the oxime concentration can lead to saturation, *i.e.* transformation of all inhibited enzymes into resulting Michaelis–Menten complexes. The oxime concentration necessary for saturation is dependent on the type of the inhibited enzyme as well as on the properties of the oxime, *e.g.* its affinity, which can be expressed by the dissociation constant K_D (*e.g.* 31 μM for obidoxime for sarin inhibited AChE[70]). In the second step, the reactivated enzyme is liberated. This reaction follows first-order kinetics and can be described by the reactivity constant k_r (*e.g.* 0.937 min^{-1} for reactivation of sarin inhibited AChE by obidoxime[70]), which can be translated easily into the reactivation half time. Notably, the velocity of this reaction, although dependent on the properties of the oxime (reactivity), is completely independent of the oxime concentration. The clinical relevance of this consideration is given by the fact that oxime concentrations resulting in about 50–70% saturation are sufficient. Higher concentrations only marginally enhance reactivation but may increase adverse events.[69] For assessment of the clinical effectiveness of a certain oxime, the reactivation half time of an oxime and the concentration necessary to achieve this half time have to be considered. It may be assumed that the shorter the reactivation half time at a tolerable oxime concentration, the more effective the oxime.

1.7.3.2 Effectiveness of Oximes in Nerve Agent Poisoning

From clinical experience of patients poisoned with parathion and treated with obidoxime, it is known that a reactivation half time of about 5 min is sufficient to achieve substantial reactivation if the poison load in the patient is not too high.[57,69,71–77] This reactivation half time can safely be achieved with ~10 μM obidoxime in parathion/paraoxon poisoned patients.[69,71,73,78] Moreover, it was

clearly shown that substantial reactivation was associated with improvement of neuromuscular transmission, indicating clinical benefit.[78–81] For ethical reasons, comparable investigations are not possible in patients poisoned by nerve agents. Hence, it appears rational to consider results from complex organ tissues and animal experiments. Indeed, in mouse diaphragms it was shown that oxime induced reactivation was accompanied by recovery of paraoxon blocked muscle force.[82,83] Using a comparable model, Seeger *et al.* showed that 30 μM HI-6 was able to restore sarin blocked human muscle force.[84] Finally, in percutaneously exposed minipigs it was shown that HI-6, in combination with cooling of the exposure site, was able to prevent inhibition of AChE by VR[85] and VX.[86] In these animals, signs of VX or VR toxicity did not become visible if HI-6 was administered as soon as red blood cell AChE activity was inhibited to 30% of its baseline activity.[86,87]

The species differences mentioned above have to be taken into account when estimating effective oxime concentrations in humans (see Section 1.2.2.1). Kinetic *in vitro* studies showed almost identical kinetic properties of erythrocyte, brain and muscle AChE when inhibited by OP and reactivated by oximes within one species.[88–94] According to these and clinical data,[78–81] erythrocyte AChE is considered to be a suitable surrogate for synaptic AChE and was used for the determination of reactivation kinetics of a larger number of OP compounds and oximes.[95] These data were used for further calculations of the relationship between reactivation half time and oxime concentration (Figure 1.2).[57,69,77]

Figure 1.2 illustrates that at low oxime concentrations, the reactivation half times increase; however, at higher oxime concentration they show asymptotic behavior, indicating that an increase in oxime concentration above a certain level (saturation, see above) no longer results in a substantial reduction in the respective half time. Moreover, although the curves behave in a roughly similar manner, the respective oxime concentrations and half times are dependent on the OP compound as well as on the oxime. As concluded from the data above, reactivation half times should be below about 10 min (*e.g.* 5 min was found to be effective for reactivation of paraoxon inhibited AChE in humans, see above). This approach allows estimation of required oxime concentrations. However, the actual use of these oxime concentrations in humans is dependent on the tolerability, which is compound dependent. Limited human data indicate that maximum oxime concentrations of ≤50 μM can be achieved after administration of one autoinjector and that these concentrations are well tolerated (see Sections 1.7.3.6–1.7.3.8). According to the data shown in Figure 1.2 obidoxime, pralidoxime and HI-6 would meet the criteria for sarin and VX, HI-6 and obidoxime for VR, HI-6 for GF, and only obidoxime for diethyl-OP pesticides. AChE can hardly be reactivated by any oxime after tabun exposure and in the case of soman, sufficient reactivation is prevented by fast aging (aging half time in humans is about 2 min). In order to visualize this, the oxime concentrations necessary to achieve reactivation half times of 5, 10 and 50 min have been calculated (see Figure 1.2) and are given in Table 1.4, with the values fulfilling the criteria marked.

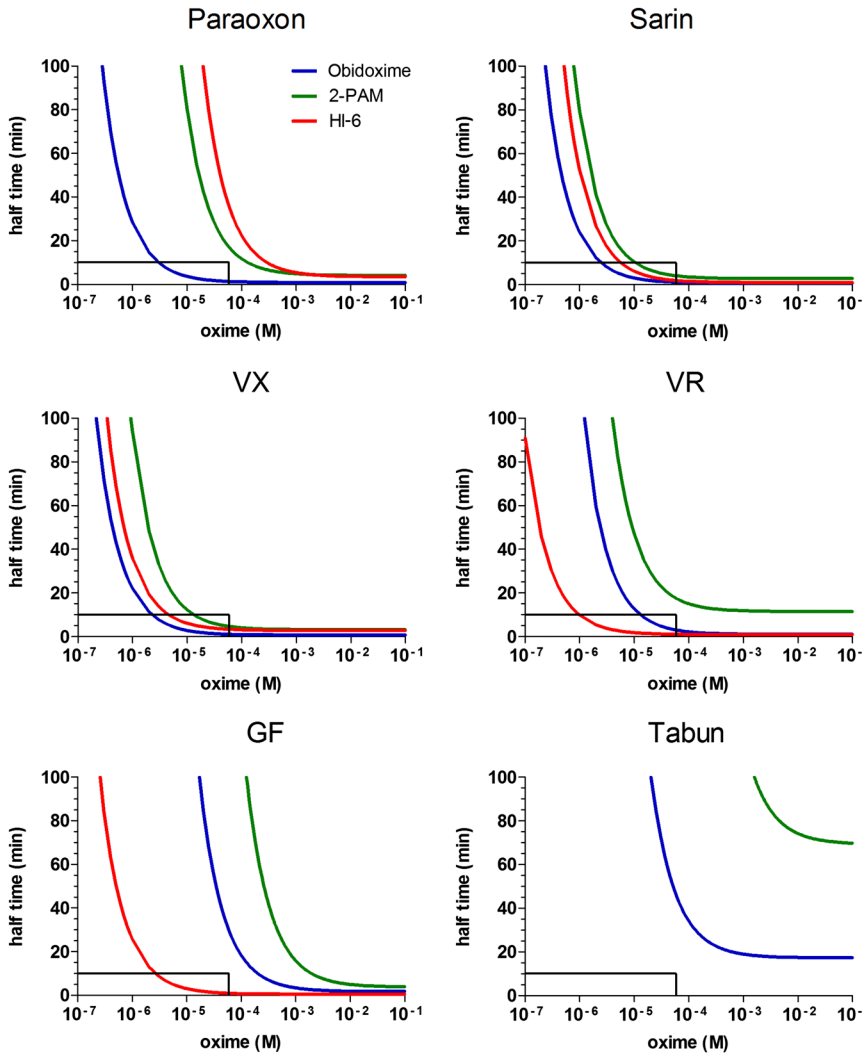

Figure 1.2 Relationship between reactivation half time and oxime concentration. Using the equation: half time = $\ln 2 \times (1 + K_D/[\text{oxime}])/k_r$, the relationship was calculated for the reactivation of red blood cell AChE under steady-state conditions with paraoxon, sarin, VX, VR and tabun, and obidoxime, 2-PAM and HI-6. The *x*-axes are plotted in log scale. The boxes highlight the clinically relevant data: oxime concentration ≤50 μM and reactivation half times ≤10 min.

Unfortunately, the kinetic constants for TMB-4 were not available and a respective calculation could not be performed. Generally, it appears that TMB-4 is a good reactivator;[96] however, its toxicity[96,97] prevents its general use. As, additionally, this oxime is not readily available on the general market, it is not considered in detail, here.

Table 1.4 Concentrations of oximes needed to achieve reactivation half times of nerve agent inhibited AChE.

	Obidoxime			Pralidoxime			HI-6		
Reactivation half time (min)	5	10	50	5	10	50	5	10	50
Sarin	5.4	2.5	0.5	34.4	10.6	1.6	12.9	5.7	1.0
Cylosarin	512	201	34.4	10 097	1943	261	5.6	2.7	0.5
Tabun	—	—	51.6	—	—	—	—	—	—
VX	5.0	2.3	0.4	50.7	13.3	1.93	15.5	4.6	0.7
VR	29.9	13.1	2.28	—	—	9.2	2.2	1	0.2
Paraoxon	6.7	3.0	0.6	828	129	41	1239	291	41

In conclusion, it cannot be assumed that a single oxime is able to reactivate AChE inhibited by all nerve agents and pesticides at tolerable concentrations. A broad spectrum of nerve agents and pesticides, however, is covered by obidoxime and HI-6. Pralidoxime is clearly a much weaker reactivator compared with obidoxime and HI-6.

1.7.3.3 Interaction with Persisting Poison Load

Pesticide poisoning teaches us that free agent (persisting poison load) may re-inhibit reactivated AChE, thereby reducing net reactivation.[57,69,73,74,76,77,81,98] This effect is clearly dependent on the concentration of the oxime and the poison.[57,69] Complete prevention of net reactivation can only be found at very high poison concentrations. In most of the cases investigated, partial reactivation was achieved and could be maintained upon continuous obidoxime infusion therapy (750 mg per 24 h, resulting in a plasma level of 10–20 μM) for several days in severely parathion poisoned patients needing artificial ventilation.[73,98] Decreasing poison load was generally accompanied by an increase in AChE activity upon continuous obidoxime treatment. Moreover, in a severely parathion poisoned patient, a prolonged aging half time (about 66 h, compared with an expected aging half time of 30 h) was recorded during obidoxime infusion.[77] This remarkable finding indicates that oxime treatment may even prolong the therapeutic window for agents that undergo fast aging. On the other hand, a fast reactivation–re-inhibiton–reactivation cycle may contribute to accelerated degradation of the poison. Such an approach may be a therapeutic option when infusing erythrocytes, *i.e.* AChE, together with an effective oxime.

Due to the rather rapid elimination of G-type nerve agents, a high and persisting poison load is unlikely. In contrast, percutaneous exposure to V-agents will result in a slow increase of agent concentration followed by a plateau for hours, or possibly days. Hence, re-inhibition due to relevant poison load will be a problem, especially in patients with initially successful oxime treatment and inadequate continuation of oxime administration.

1.7.3.4 Oxime Dosing Strategies

Finally, the question on the dose of the oxime remains. When using autoinjectors (single bolus dose, *e.g.* 220 mg obidoxime, 600 mg pralidoxime or 500 mg HI-6), maximum concentrations of ~40 μM for obidoxime, and ~50 μM for pralidoxime and HI-6 can be expected,[71] with elimination half times of approximately an hour (1.4 h for obidoxime, 1.3 h for pralidoxime and 1.0 h for HI-6[71]). These doses should allow sufficient reactivation in sarin inhalation poisoning in military or terrorist scenarios as outlined above. In contrast, obidoxime and pralidoxime may be only marginally effective in GF poisoning and HI-6 would be better. Using three autoinjectors simultaneously would result in maximal concentrations of about 120 μM for obidoxime, 145 μM for pralidoxime or 155 μM for HI-6.[71] Under such conditions, in GF poisoning reactivation half times of 14 min for obidoxime and 85 min for pralidoxime at the maximal concentration can be estimated. Aside from the highly effective HI-6, at the most obidoxime could reactivate GF inhibited AChE under such conditions. Due to the expected short half time of G-agents under the conditions considered, one autoinjector filled with an effective oxime should be sufficient in most cases. In severe cases, repetitive doses may be appropriate; the necessity of an infusion therapy should be the exception. In tabun poisoning no effective reactivation may be expected and in soman poisoning fast aging will prevent reactivation under realistic conditions.

Reactivation of V-agents needs a different assessment. Generally, obidoxime, HI-6 and pralidoxime appear to be good reactivators for VX, while pralidoxime appears less efficient in VR poisoning. Slow and progressive inhibition of AChE was shown in percutaneous VX poisoning, which opens a therapeutic window for oxime administration prior to the onset of signs of poisoning. Indeed, in swine percutaneously exposed to VX and treated with repetitive HI-6 injections when red blood cell AChE activity had dropped to approximately 30% that of controls, severe signs of poisoning could be prevented until the end of the experiment (6 h).[99] These data emphasize the need to start oxime therapy as early as possible and to continue oxime administration, either by repetitive bolus injections or by continuous infusion, for as long as free agent is circulating in the body. Generally, it appears preferable to maintain an effective concentration by infusion[100] rather than having oscillating concentrations, thereby preventing concentrations from falling below the effective concentration for a certain time period.[101] A bolus dose of obidoxime, *e.g.* 220 mg (the amount in an autoinjector) or 250 mg (the amount in commercially available ampoules), should be followed by 750 mg per 24 h resulting in a plasma level of 10–20 μM. This dose regimen is licensed by the German authorities (BfArM). For pralidoxime, aside from autoinjectors (bolus doses of 600 mg pralidoxime per autoinjector), a bolus dose of 30 mg kg^{-1} followed by continuous infusion of 8–10 mg kg^{-1} h^{-1} [57,102] was recommended for OP pesticide poisoning, resulting in plasma concentrations of 80–100 μM.[57] No human safety data on HI-6 doses above 500 mg of the dichloride salt are available, making it difficult to recommend an infusion.

1.7.3.5 Monitoring of Oxime Therapy

These considerations allow definition of the following prerequisites for an effective oxime treatment:

- Reactivation of inhibited AChE with the oxime of choice is possible
- Aging does not prevent substantial reactivation
- Net reactivation is not prevented by re-inhibition due to a high poison load
- Oxime therapy is maintained for a sufficient period of time
- Oxime is administered at a dose that results in an effective concentration

To assess these prerequisites, the laboratory determination of cholinesterase status, described in Chapter 5 can be used. Activity of red blood cell AChE or plasma BChE are suitable parameters for laboratory confirmation of an exposure to OP compounds. Measurement of the reactivatability (incubation of a patient's blood dilution with a specified oxime concentration for a defined period of time followed by determination of AChE activity) allows assessment as to whether reactivation is possible at all or whether aging has occurred. Measurement of the inhibitory activity (incubation of a patient plasma sample with test AChE for a defined time period followed by determination of AChE activity) enables a rough estimation of the poison load in the patient. When reactivation is possible but the poison load is high, net reactivation is prevented and red blood cell activity remains inhibited.

These parameters enable a rough estimation of the period over which oximes should be administered. In conclusion, oxime therapy should be maintained for as long as reactivation is possible and as long as inhibitory activity is present in the patient's blood.

1.7.3.6 Obidoxime

Obidoxime was synthesized by Lüttringhaus and Hagedorn in 1964,[103] and many European countries have currently fielded obidoxime for military use as well as in the civilian sector.[54]

The recommended obidoxime plasma level for effective reactivation of nerve agent and OP pesticide inhibited AChE is 10–20 μM (see above).[57,104] This recommendation is based on experimental findings[95,98] and substantiated by clinical data from OP pesticide poisoning.[69,73,74,77–81,81,105] Using an autoinjector, *e.g.* ATOX II filled with 220 mg obidoxime, a maximum plasma concentration of about 40 μM may be estimated.[98] With an elimination half time of about 1.4 h, an appropriate concentration (above 10 μM) can be maintained for 2–3 h. If obidoxime is needed for a longer period, a repetitive bolus dose, or better, a continuous infusion can be used. The established therapeutic regime of an initial i.v. bolus of 250 mg obidoxime followed by continuous administration of 750 mg per 24 h obidoxime was derived based on pharmacokinetic data, assessed in healthy male volunteers.[57,101] Retrospective

pharmacokinetic studies of poisoned patients confirm the achievement of the targeted obidoxime plasma level in this regimen.[106] Early recommendations or attempts to administer repetitive bolus doses up to 6 g per day can be regarded as obsolete (see above).

The use of obidoxime chloride was investigated in healthy volunteers in the 1960s and 1970s.[107–109] Generally, single doses up to 10 mg kg^{-1} were well tolerated. A peculiar side effect was reported by Sidell[107] as a generalized warmth that became localized in the skin around the mouth as well as inhibition of face muscles and a menthol like sensation within 15 min of a 250 mg obidoxime i.m. injection. Later, a menthol like sensation in the rhino-pharyngeal space during inspiration was experienced.[107,108] When the dose was increased (>10 mg kg^{-1}), in addition to dry mouth, a hot feeling in the throat, experiences of paresthesia, a transient mild to moderate increase of systolic and diastolic blood pressure (~11–17 mmHg), and increased heart rate (30 beats per min) occurred.[107] In a study targeting side effects on the liver after two injections of 250 mg obidoxime i.m., no hepatotoxic effect was recorded.[110] At higher doses, some authors associated hepatic dysfunction in terms of cholestatic icterus and elevation of liver enzymes with obidoxime administration in OP pesticide poisoning.[111–114] Indeed, after high dose obidoxime treatment, *e.g.* 7.7 g over 3 days (day 1: 16 × 250 mg, day 2: 9 × 250 mg, day 3: 6 × 250 mg) and 6.75 g over 3 days, in two patient with severe parathion poisoning, transient signs of cholestasis occurred, while in one patient treated with 750 mg no signs of hepatotoxicity were registered.[112] Von Gaisberg and Dieterle reported on a parathion poisoned patient who had been treated with 22 ampoules of obidoxime within a short time. The patient similarly developed signs of cholestasis that ameliorated during ongoing therapy.[113] In a retrospective study by Finkelstein and colleagues,[114] 5 (9.4%) out of 53 organophosphate poisoned patients receiving the highest cumulative doses of obidoxime (6 mg kg^{-1} every 4 h) suffered from impaired liver function that returned to normal within 3–5 weeks. Moreover, in this study, several patients developed cardiac arrhythmias. In these patients, frequency of cardiac arrhythmias correlated with the doses of both antidotes when the highest doses of atropine and obidoxime were administered. In patients receiving low obidoxime doses but high atropine doses, frequency of cardiac arrhythmias were correlated with the atropine dose. Finally, in patients developing prolongation of the Q-T interval, no correlation to the obidoxime dose could be found.[114] Prinz[115] reported on a parathion poisoned patient treated with 3 × 250 mg obidoxime and elevated liver parameters were recorded. Detailed investigation, however, revealed that these parameters were most probably due to recent viral hepatitis.[115] Finally, in a study using 250 mg obidoxime as bolus followed by 750 mg per day for a severely organophosphate poisoned patients no obvious hepatic toxicity was correlated with obidoxime. Here, elevations of serum transaminases were mild to moderate and transient, often subsiding during ongoing obidoxime therapy.[116] Thereby, hepatotoxicity was assessed thoroughly in patients who died in this study but no correlation to obidoxime treatment could be found.[116]

In conclusion, the administration of a bolus dose of 250 mg obidoxime as well as a dose regimen using 250 mg obidoxime, followed by 750 mg per day appears to be safe. Both dose regimens are covered by the license of BfArM.

1.7.3.7 Pralidoxime

Pralidoxime was developed in the 1950s by Wilson and colleagues.[49,117,118] Four salts of pralidoxime are in clinical use for antidotal treatment of OP poisoning, pralidoxime chloride (2-PAM, molecular weight 172.6 Da), pralidoxime iodide (molecular weight 264.1 Da), pralidoxime methanesulfonate (P2S, molecular weight 232.3 Da) and pralidoxime methylsulfate (Contrathion, molecular weight 248.3 Da). The chloride salt is used widely, whereas P2S and Contrathion are used only in a few countries such as France, Belgium and the UK.[96,119] It should be mentioned in particular that pralidoxime iodide may cause thyroid toxicity if given for a long period. The concentrations given above refer to pralidoxime chloride if not indicated otherwise.

Autoinjectors are available filled with, for example, 600 mg pralidoxime chloride, 500 mg pralidoxime methanesulfonate[120] or 350 mg of pralidoxime methyl sulphate.[121] Healthy young volunteers administered with doses of up to 10 mg kg^{-1} i.m. or i.v. experienced a slight and transient increase in heart rate (about 10 beats per min) that lasted for about half an hour.[122] Blood pressure was not affected significantly.[122] Mild and transient symptoms of dizziness, double and blurred vision, and diplopia were recorded.[122] When higher doses were administered (15–45 mg kg^{-1} i.v.), pralidoxime clearly showed cardiovascular activity. A period of marked increase in systolic and diastolic blood pressure was followed by a period of hypotension 3–4 h later. Heart rate was not changed significantly.[123] Dizziness, blurred vision, diplopia were also recorded when 15–30 mg kg^{-1} pralidoxime iodide[124] or pralidoxime methanesulfonate[125] was administered to healthy volunteers. Medicis and colleagues[126] compared administration of 16 mg kg^{-1} pralidoxime chloride i.v. over 30 min (traditional short infusion) with a regimen consisting of a loading dose of 4 mg kg^{-1} over 15 min followed by 3.2 mg kg^{-1} h^{-1} for 3.75 h (total dose 16 mg kg^{-1}). It turned out that the loading dose regime was clearly better tolerated. Dizziness and blurred vision occurred only in the traditional short infusion group. Apart from a significant increase in diastolic blood pressure in the traditional short infusion group when compared with the loading dose group, no further cardiovascular effects were reported.[126] Notably, a maximum concentration of 14 μg l^{-1} (80 μM) pralidoxime chloride was achieved with the level above approximately 60 μM for about an hour in the traditional group (data estimated from the graph shown in the manuscript[126]), while in the loading dose group, a permanent level of about 10–30 μM was maintained. Both rapid i.v. injection of pralidoxime [both iodide (0.6–1.0 g i.v.; 1–4 injections per day) and chloride (0.5–1.0 g i.m.; 1–4 injections)] and high doses (not specified) were associated with transient impairment of respiration[97] in OP pesticide poisoned patients. One severely coumaphos poisoned patient even experienced cardiac arrest (asystolia) after

administration of 2 g pralidoxime iodide over 10 min.[127] It remains unclear whether a small amount of narcoleptics (self medication with tranquillizers) or hydrocarbons from the solvent contributed to this serious adverse event in the patient.[127] In a therapeutic accident, approximately 4–5 g of pralidoxime chloride was infused rapidly within 10–20 min to a patient who was just recovering from OP compound poisoning treated successfully with pralidoxime. He developed blurred vision, rigidity of extremities, neurological disorders, substantial increase in blood pressure (190/110 mmHg) and tachycardia (116 beats per min). Finally, the patient needed artificial ventilation and sedation. Nevertheless, he could be discharged from the hospital after an uneventful recovery.[128]

Substantially higher doses of pralidoxime are recommended in OP pesticide poisoning[57,101,129,130] since the previously proposed concentration of 4 μg ml^{-1} was considered inappropriate. Eddleston and colleagues administered a 2 g pralidoxime chloride loading dose over 20 min followed by constant infusion of 0.5 g h^{-1} for a maximum of 6 days[53] to OP pesticide poisoned patients and compared them to saline administered controls. The pralidoxime regimen resulted in a plasma level of about 100 μM. Although clear reactivation could be shown in patients poisoned by diethyl- and dimethyl-type OP pesticides, this finding was not correlated with a better survival rate. Regarding analysis of adverse events, a significant increase in blood pressure and tachycardia was reported in the pralidoxime group during the first 3 days. The reason for the failure of clinical benefit despite substantial reactivation was not analyzed in detail.[53] Goel and colleagues[131] showed clear regeneration of red blood cell AChE activity in eight OP pesticide poisoned patients following pralidoxime infusion over the first 24 h after exposure. However, probably due to the small number of patients, a better survival rate could not be shown in this study, either. In contrast, in other studies using either a high pralidoxime dosing regimen of 1 g pralidoxime infusion every hour (24 g per day), compared with 1 g every 4 h (6 g per day) after a 2 g loading dose,[132] or a dosage regimen tailored to the severity of poisoning and the level of BChE activity,[133] there was a clear benefit for morbidity and mortality. Accordingly, there is an ongoing debate on the effectiveness of oximes in OP pesticide poisoning and adequate studies are urgently needed (see above).

From the aspect of safety, autoinjector doses appear to be safe in adults. For children, a dose correction appears necessary. When using higher pralidoxime doses, *e.g.* according to the World Health Organization (WHO) recommended regimen (30 mg kg^{-1} pralidoxime chloride bolus followed by 8 mg kg^{-1} h^{-1} infusion) in severe nerve agent poisoning with persisting poison load as assumed in VX poisoning, adverse events may develop.

1.7.3.8 HI-6

Despite its experimentally proven antidotal efficacy in the treatment of nerve agent poisoning, HI-6 is not yet licensed for clinical use. One major problem appears to be the production of large quantities of good manufacturing

practice grade HI-6. Another important limitation of HI-6 use is its poor stability in aqueous solutions[134,135] and the low solubility of the dichloride salt at low temperatures.[136,137] In particular, the latter feature requires relatively sophisticated dry–wet autoinjectors.[136–139] Nevertheless, HI-6 is available for military use in some countries such as the Czech Republic, Sweden and Canada.

Several studies have examined the safety of HI-6 administration. Single doses of up to 500 mg kg^{-1} HI-6 dichloride turned out to be well tolerated in humans. No adverse effects concerning the cardiovascular, respiratory, central nervous system, muscle or visual function have been reported after use of HI-6.[56,140,141] During treatment of OP poisoned patients i.m. administration of 500 mg HI-6 was conducted four times a day up to a cumulative dose of 14 g, no adverse effect occurred that could be related to the oxime.[56] These data indicate that HI-6 dichloride might be more tolerable than pralidoxime and obidoxime.

1.7.3.9 Benzodiazepines

One feature of nerve agent poisoning is the development of central over-excitation. Clinically, this feature is characterized by central seizures [identified by electroencephalography (EEG)] and convulsions (outward manifestations; for review see ref. 142). Extensive research was undertaken to improve therapy of nerve agent induced seizures (for review see ref. 142–144). Generally, this research is based on animal and *in vitro* experiments, mainly focused on poisoning with soman. It is assumed that the course of seizure development can be divided into three phases: (i) a short cholinergic phase; (ii) a transitional phase characterized by high cholinergic activity and increasing glutamatergic activity; and (iii) a predominate glutamatergic phase.[144] Therapeutic problems arise when initial therapy is delayed and anticholinergic drugs are no longer effective. In the past decades, a huge variety of established and experimental drugs were tested to counteract nerve agent induced seizures and convulsions. Unfortunately, all of these experiments were done *in vitro* or in animals, and it remains uncertain whether, or in which way, these results can be extrapolated to humans.

Clinical reports on convulsions in nerve agent poisoning are rare. Foroutan[10] reported that he used diazepam, which was the only anticonvulsant available in chemical emergency units during the Iran–Iraq war. Therefore, diazepam was not only used as classical anticonvulsant but also during the "spastic stage" that was seen during recovery from sarin poisoning. No EEG recordings were available for these incidents.

Later on, during the Japan (Matsumoto in 1994 and Tokyo in 1995) sarin attacks, diazepam was used successfully. Yanagisawa *et al.* reported that severely poisoned patients, who had survived the attack in Masumoto but suffered from loss of consciousness and generalized seizures, had been treated successfully with atropine, benzodiazepines, i.v. fluids and other systematic therapies.[145] In the patients treated at St Luke's International

Hospital, Tokyo, Japan, after the sarin attack, convulsions were rare events (three patients, 2.7%).[41] These patients were supplied with atropine, pralidoxime and diazepam. It appeared that pralidoxime and diazepam reduced the frequency and severity of convulsions and fasciculations, although it was difficult to distinguish between convulsions and fasciculations in unconscious patients.[41]

When looking at patients with OP pesticide poisoning there is a comparable pattern. There are no randomized clinical trials or cohort studies on benzodiazepines in the treatment of acute OP pesticide poisoning.[102] However, benzodiazepines, such as diazepam, lorazepam and midazolam, are recommended.[102] Based on observations of single patients in medically controlled scenarios, Zilker[25] even suggests to start early with low doses of diazepam in anxious patients with mild signs of OP pesticide poisoning. If adequate artificial ventilation is not possible due to severe spasm, relaxation (*e.g.* by pancuronium) may be necessary.[25] Midazolam and fentanyl are considered appropriate for prolonged sedation of artificially ventilated patients.[25] Inadequate responses of severely poisoned patients to benzodiazepines requires the use of barbiturates.

The US military field autoinjectors contain 10 mg of diazepam (labelled CANA) as an anticonvulsive antidote against nerve agents.[33] It is, however, assumed that higher doses, *e.g.* up to 30–40 mg could be necessary.[33] This recommendation is in accordance with the one given by Balali-Mood and Saber, *i.e.* 5–10 mg diazepam i.v. in the absence of convulsions and a bolus of 10–20 mg i.v. in the presence of convulsions.[46] Balali-Mood and Saber further suggest that the dose of diazepam recommended by WHO of 5–10 mg i.v. over 3 min can be repeated every 10–15 min in adult patients up to a maximum of 30 mg.[46]

McDonough and colleagues have shown in guinea pigs that midazolam is able to stop seizures fast and at a lower dose compared with other benzodiazepines (avizafone, clonazepam, diazepam and lorazepam).[146] Accordingly, midazolam appears to be an alternative to diazepam in nerve agent poisoning. However, midazolam may induce respiratory depression, which may limit its use in the field.

In conclusion, diazepam remains the recommended drug for the emergency treatment of organophosphate induced seizures and convulsions.

1.7.3.10 Magnesium

Magnesium (Mg), one of the most abundant cations in the body, is distributed up to 99% intracellularly, including in the skeleton.[147] Mg in bone belongs either to the mineral lattice or to an elutable surface limited mineral pool that may serve as a reservoir for the maintenance of constant plasma concentrations. The normal serum concentration of Mg^{+} amounts to 1.5–2.5 mEq l^{-1} (1.8–3.0 mg dl^{-1}), of which about a third to a half is bound to plasma proteins.[148] Its plasma concentration is tightly held within the normal range by the kidneys.[147] Mg has an elimination half time of about 4 h (product

information: $MgSO_4$, 2015) and roughly 80% of an i.v. Mg load is excreted in the urine within 24 h after admission in healthy subjects.[147]

Mg has been proposed as an adjunct to conventional therapy in OP poisoning.[149,31] Pajoumand presented a study on OP pesticide poisoned patients treated, in addition to conventional therapy, with Mg ($MgSO_4 \cdot 7H_2O$, at a dose of 4 g per day i.v.). The mortality in 11 patients with OP poisoning was lower and the hospital stay shorter than in the group without Mg administration, but neither type nor dose of OPs ingested were provided and only a small amount of data on clinical course during therapy (*e.g.* markers for severity, complications, cause of death and time of death) could be found. In addition, 82% of the patients were treated with obidoxime in the $MgSO_4$ group but only 55% in the group without $MgSO_4$ therapy. Thus, a better rate of reactivation achieved by obidoxime when compared with pralidoxime could also be the reason for the different outcome.[149]

Moreover, a conclusive explanation for the potential beneficial effect of Mg is not established. Pajoumand and colleagues[149] refer to a study by Petroianu *et al.*[150] that showed, in artificially ventilated and anaesthetized minipigs, an excessive increase in blood pressure and heart rate as well as a drop of hematocrit could be prevented upon $MgSO_4$ infusion over 150 min in control animals as well as in animal poisoned by paraoxon (54 mg kg^{-1}). The dose of $MgSO_4$ and fluid used to achieve this effect, however, was significantly higher in the poisoned animals.[150] In conclusion, the study of Petrouianu cannot be used as an explanation for the beneficial effects in the Pajoumand study (no data on blood pressure, heart rate or hematocrit were provided). Moreover, in human poisoning, cardiovascular failure and respiratory depression appear to be life threatening for a long period (*e.g.* several days) after $MgSO_4$ administration.

Another possible explanation for a potential beneficial effect could be alleviation of seizures arising during OP poisoning. Administration of $MgSO_4$ in order to achieve a continuous plasma level of about 3.5–7 mEq l^{-1} (4.2–8.4 mg dl^{-1}) is recommended for the treatment of eclamptic convulsions.[148] The situation for pregnant woman and the different mechanism discussed in this special context (for review see ref. 148), however, cannot be transferred to human OP pesticide poisoning without detailed scientific assessment. Pajoumand *et al.* do not provide further data on possible seizures. Moreover, Katalan and colleagues[151] investigated the effect of Mg in sarin poisoned rats treated with atropine, TMB-4 and $MgSO_4$. They concluded that there is no advantage in using $MgSO_4$ as an anticonvulsant in antidotal treatment against warfare agents such as sarin.[151]

The effect of Mg on neuromuscular function has been known since the 1950s.[152] Since Mg is able to reduce the stimulating effect of ACh on muscles, it was obvious to investigate whether such an effect may be beneficial in OP poisoning. Singh and colleagues performed the decisive study,[153] investigating the effect of $MgSO_4$ (4 g i.v.; 20% $MgSO_4 \cdot 7H_2O$) in OP pesticide poisoned patients who were initially treated with appropriate atropine doses and pralidoxime. Although the group could detect a slight effect on the pattern of

neuromuscular transmission, they clearly pointed out that they had not found any indication of improvement in any clinical parameters and concluded that it is unlikely that $MgSO_4$ is therapeutically beneficial in acute OP poisoning.

Finally, $MgSO_4$ (20% $MgSO_4 \cdot 7H_2O$) was administered to four dosing groups [4 mg i.v. (n = 16), 8 mg i.v. (n = 8), 12 mg i.v. (n = 8) or 16 mg i.v. (n = 8)] in OP poisoned patients.[154] In this study, no adverse events of $MgSO_4$ were observed. As this study assessed the safety of $MgSO_4$, no analysis of the beneficial effects of $MgSO_4$ was performed. For such an assessment, a higher number of patients would have been necessary.[154]

In conclusion, although Mg appears to be well tolerated in OP poisoned patients, a clear beneficial effect has not been demonstrated so far. Thus, the administration of $MgSO_4$ cannot be recommended in nerve agent poisoning at present. This assessment is in agreement with the analysis of Blain.[102]

1.7.3.11 Alkalinization by Sodium Bicarbonate

As early as 1983, Cordoba and colleagues investigated modifications of the acid–base equilibrium and use of sodium bicarbonate as an aid in the treatment of toxicity in dogs poisoned with a LD_{100} of DDVP (*O*–*O*-dimethyl 2-2 dichlororine vinylphosphate).[155] They reported that upon treatment with sodium bicarbonate, a recovery of the acid–base balance and survival of 84.4% of the dogs were achieved. Since then, the effect of sodium bicarbonate has been investigated in a few studies in rats also poisoned by DDVP.[156,157] In the investigation of Bajgar and Portman, also on DDVP in rats, the nerve agent sarin and pyridostigmine were included when the effects of sodium bicarbonate were assessed.[158] Moreover, some case series or clinical trials[156,159,160] have been published in which patients poisoned by various pesticides, in addition to conventional treatment (atropine/atropine in combination with an oxime), were administered sodium bicarbonate in order to achieve alkalinization.

All of the authors came to the conclusion that alkalinization by sodium bicarbonate has a beneficial effect in OP poisoning. However, the highest benefit was achieved when sodium bicarbonate was administered in combination with standard antidotes (*e.g.* atropine or atropine in combination with an oxime).

Although no clear mechanism has been established, several mechanisms have been suggested to explain the beneficial effect: enhanced clearance of the poison from the body; improved efficacy of oximes; a direct effect on neuromuscular function; volume expansion with improved tissue perfusion; and bicarbonate induced release of lactate into the circulation.[161]

Furthermore, increased enzymatic and chemical hydrolysis of OP compounds by sodium bicarbonate was proposed.[160] However, it is rather unlikely that a small pH shift from 7.36 to 7.48 would increase the hydrolysis of an agent to such an extent that a substantial reduction of the body load could be achieved. In particular, the chemically and biologically stable V-agents would need harsher conditions for detoxification.[162,163]

On the other hand, severe OP poisoning may result in acidic conditions,[160] which must be corrected by moderate alkalinization. In this respect, appropriate administration of sodium bicarbonate should have a therapeutic value without interfering with the OP compounds themselves.

In conclusion, there are inadequate scientific and clinical data to support alkalinization in nerve agent poisoning.

1.7.3.12 Supportive Treatment

The clinical picture of nerve agent poisoning is mainly dominated by cholinergic crisis. When the administration of atropine, an oxime and a benzodiazepine are not able to antagonize the clinical effect, further supportive measures have to be taken.

At first, it is crucial to maintain sufficient ventilation. On the spot, assisted or artificial ventilation has to be started as early as possible. Mouth-to-mouth ventilation has to be avoided. When the patients are transported to medical facilities, established ventilation protocols should be followed. Special care has to be taken of severe bronchospasm, marked bronchosecretion and pulmonary edema.[164] Similar protocols as used for OP pesticide poisoned patients could be used (see above).

Other complications, *e.g.* pneumonia and circulatory depression, have to be treated with standard emergency or intensive care protocols.

1.8 Summary and Outlook

Although the Chemical Weapon Convention came into force in 1997, the recent events in the Middle East clearly show that chemical warfare agents remain a threat. Thereby, possible scenarios are no longer mainly restricted to typical military confrontations but are now extended to asymmetric conflicts and terrorist attacks. In any case, if such an event occurs one has to expect a large number of patients calling for medical care. In particular, nerve agents are most dangerous due to their high toxicity.

To apply adequate treatment, medical personnel, equipment and facilities need protection. However, because especially volatile nerve agents lead very quickly to life threatening signs and symptoms, fast treatment will be necessary. Accordingly, diagnostic and therapeutic measures have to be provided while wearing protective clothing until the patients undergo decontamination.

The trigger to treat will be clinical diagnosis, based on the typical signs and symptoms of cholinergic crises. Inhibition of red blood cell AChE can be assessed on site and can confirm poisoning by anticholinergic compounds within several minutes. For treatment, atropine and an oxime are first line drugs. Atropine has to be applied rapidly and at a sufficient dose, *e.g.* starting with 2 mg and doubling the dose every 5–10 min until relief of cholinergic signs and symptoms. In severe cases, a continuous infusion may be

necessary. Similarly, oximes, *e.g.* obidoxime, pralidoxime or HI-6, have to be injected as soon as possible. Oximes are used to resolve the nerve agent induced inhibition of AChE, thereby acting as causal antidotes. To achieve this goal, appropriate dosing is necessary as well as continuation for an adequate time period, which is dependent on the amount of poison absorbed as well as on the persistence of the poison in the body.

Unfortunately, under several circumstances, sufficient reactivation will not be possible, *e.g.* when the time to treatment is delayed (*e.g.* soman) or the nerve agent induced inhibition of AChE cannot be reactivated substantially by oximes (*e.g.* tabun). In such cases, supportive measures, *e.g.* artificial ventilation, will become decisive.

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