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Practical Guidelines for Acute Care of Victims of Bioterrorism: Conventional Injuries and Concomitant Nerve Agent Intoxication

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THE potential use of weapons of mass destruction has recently become a real threat even in regions of the world that are remote from areas of ongoing armed conflicts. Episodes of the use of sarin or VX, both potent acetylcholinesterase (AChE) inhibitors that cause cholinergic crisis, in the terrorist attacks against civilians in Japan in 1994 and 1995 which produced several fatalities and hundreds of casualties,[1,2] and the military use of nerve agents (NA) by Iraq against Iran and the Kurdish population during the 1980s are grim examples of the deadly potential of NA.

Victims of a mass casualty event can suffer from physical trauma alone or from trauma in combination with gas intoxication. The exposure of a physically injured patient to a toxic substance, in a scenario of mass injury, has recently gained major attention among planners of future protocols for emergency medical services.[3] Furthermore, when a civilian population becomes the prime target of an NA attack, diversity in age and previous health status are expected to increase the extent of the injuries compared with those of healthy adult soldiers by as much as 10-fold.[4] Because rapid deterioration and multiorgan involvement are to be expected after a physically injured individual is exposed to a toxic substance, proper organization and complex but efficient acute medical and surgical care systems must be organized and deployed to ensure a maximal number of saved lives.

The various national rescue forces that have traditionally been tasked with models of rapid evacuation and decontamination of large numbers of poisoned civilians from affected areas appear to be only a fraction of future necessities.[5] The proposed management of mass casualty events needs to be based on triage principles and acute care measures. These should include: rapid identification of the offending agent, swift decontamination by well-protected emergency medical personnel, and triage-guided mass evacuation to a nearby medical facility that should be well equipped and staffed with personnel who have been properly trained to deal with such multifaceted events.

The specifics of the administration of acute care and anesthesia in combined physically traumatized and intoxicated individuals have not been previously addressed in depth. These victims will inevitably require urgent surgical intervention and prolonged perioperative acute care.[6] Understanding the interdependence between the toxic and the traumatic occurrences and the drugs that are used to prevent or treat NA intoxication [pyridostigmine bromide, a reversible inhibitor of acetylcholinesterase (AChE)[7]; atropine, a muscarinic receptor antagonist, which is one of the on-site first-aid pharmacological resuscitation drugs; and oxime-like pralidoxime chloride, HI6 or obidoxime chloride (all AChE reactivators)][6,8] is vital. In addition, the administration of anesthesia and emergent surgery pose further unpredictable threats to the central nervous system (CNS), the cardiovascular system, and to respiratory function, all of which may be compromised after chemical intoxication and physical trauma. When both insults take place simultaneously, they are highly likely to potentiate each other's detrimental effects and severely compromise the patient's condition. Noteworthy, information concerning the effects of NA intoxication in humans is largely derived from reports of incidents of intentional terrorist attacks or of accidental exposure to pesticide organophosphate poisoning, compounds that are chemically related to NA albeit with lower toxicity.[9]

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Table 1. Toxicologic Properties of Nerve Agents

Agent	LCt_{50} (mg · min^{-1} · m^{-3})	LD_{50} (mg)
Tabun	400	1,000
Sarin	100	1,700
Soman	50	100
VX	10	10

LCt_{50} = the product of the concentration of nerve agent in air and the time that is needed until it kills 50% of an unprotected population inhaling the agent; LD_{50} = dosage that would kill one half of unprotected victims through subcutaneous exposure.

This review describes the neuropharmacological interrelationship of NA and their antagonists aiming at examining anesthetic compounds and techniques that would be useful during the period of critical care delivery. Topics such as hospital and authority preparedness have been extensively reviewed elsewhere[10–12] and are not covered in this review in which the focus is on modes of handling chemically intoxicated and physically traumatized patients.

Nerve Agents

History. Nerve agents (NA) were originally synthesized shortly before World War II by German scientists attempting to develop superior pesticides based on existing organophosphate compounds.[13] Tabun was the first to be synthesized, followed by sarin and soman, which were produced at the end of 1944. When the Allied forces occupied Germany and seized local research and production sites, the code names of GA, GB, and GD were given to tabun, sarin, and soman, respectively. Another type of NA is VX, which was originally discovered in the UK while searching for new insecticides and was later tested by the Chemical Corps in the United States. They found it more persistent and much more toxic than the G-series agents. The production of the VX series, named so for its venomous nature, was halted by President Nixon in a special executive order following an accidental leakage from an aerial spray tank that killed 6,000 sheep.[13]

Chemical Features

Nerve agents are considered to be the most dangerous of all chemical weapons and among the most lethal compounds known to mankind. For example, the lethal concentration time (LCt_{50}) for VX is 500 times less than hydrogen cyanide, a highly toxic compound (table 1).[14] Tabun, sarin, and soman (the "G-agents") are actually fluorinated cyanide-containing organophosphates. They are colorless and odorless volatile liquids whose vapors are heavier than air so that they tend to gravitate to the ground. The "V-agents" (VX) are sulfur-containing organophosphates, which are less volatile and more enduring, and mainly constitute a liquid contact hazard. The amount, duration, and route of exposure to NA are important factors in determining the clinical course of intoxication. Respiratory symptoms (shortness of breath, wheezing, and bronchorrhea—all muscarinic effects) are the early manifestations of vapor exposure, followed by progressive muscle weakness, leading to cardiorespiratory collapse and death within minutes. In contrast, dermal exposure leads mainly to early local muscle twitching (nicotinic effects), which, depending on the dose, can progress to fasciculation, weakness, and delayed complete paralysis. Dermal exposure generally produces a more gradual progression of the respiratory symptoms, but it constitutes a more significant risk to healthcare personnel should there be a direct contact with contaminated clothing and skin. In either case, respiratory failure develops and ultimately leads to death.

Pharmacology and Mechanisms of Action

Nerve agents can affect almost all organ systems but their high lethality stems from their capacity to cause paralysis of the respiratory muscles and severe depression of the CNS (table 2). Unlike the temporary effect of organophosphate compounds, NA cause irreversible inhibition of various types of AChE through a covalent binding to the enzyme active site (fig. 1).[9] The enzymatic inhibition takes place in the central and peripheral nervous systems, and its effect can be estimated by measur-

Table 2. System-oriented Clinical Manifestations of Nerve Agent Intoxication

System	Clinical manifestations
Central nervous	Seizure, coma, respiratory depression
Cardiovascular	Initial nicotinic sympathetic hyperstimulation (tachycardia, hypertension) followed by muscarinic activation (bradycardia, heart block, prolongation of QT, arrhythmias, and hypotension)
Respiratory	Laryngeal and upper airway irritation and congestion, bronchorrhea, bronchospasm (muscarinic effects), respiratory muscle paralysis (nicotinic effects), and pulmonary edema
Musculoskeletal	Involuntary fasciculation followed by weakness and flaccid paralysis (nicotinic effects)
Gastrointestinal	Hypermotility causing nausea, vomiting, abdominal cramps, and severe diarrhea (muscarinic effects)
Urinary tract	Urinary incontinence (muscarinic effects)
Secretory glands	Excessive lacrimation, salivation (muscarinic effects), and perspiration (muscarinic effects secondary to ganglionic stimulation by acetylcholine)

Clinical manifestations result from intense cholinomimetic poisoning as a result of an excess of acetylcholine in the central, peripheral, and autonomic nervous systems. Visceral smooth muscle, cardiac muscle, and the secretory glands are influenced through muscarinic hyperstimulation (antidotal treatment: atropine), whereas autonomic ganglia and skeletal muscle are affected due to nicotinic hyperstimulation (antidotal treatment: oximes).

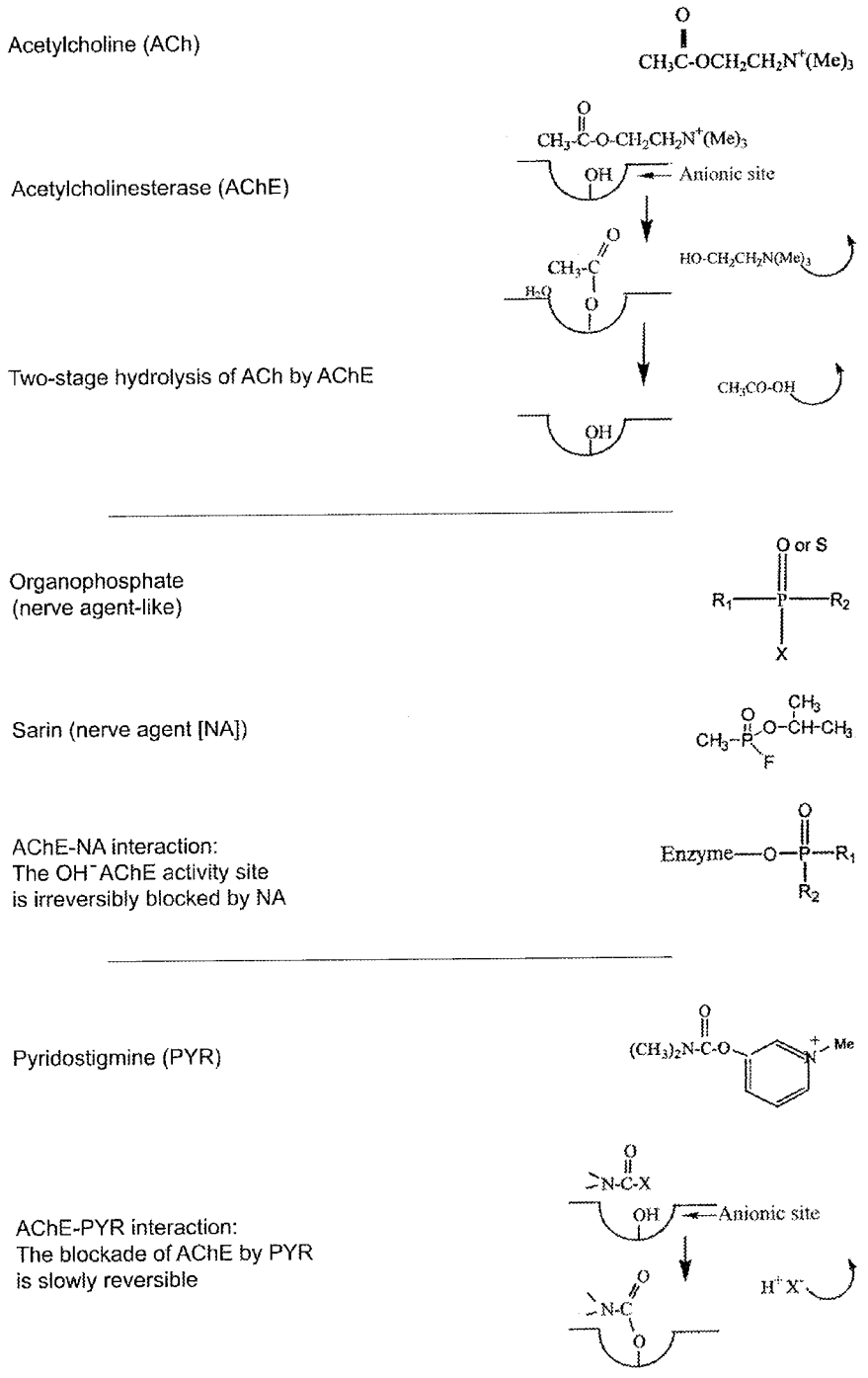

Fig. 1. Chemical interactions between acetylcholinesterase and acetylcholine, organophosphate, nerve agents, and pyridostigmine.

ing AChE activity in red blood cells (RBCs).[15] This measurement is an approximation of the activity of AChE in the CNS and can roughly indicate the degree of toxicity. Current clinical laboratory tests cannot directly measure serum or urine concentrations of NA or their metabolites.

The resultant block of the hydrolysis of acetylcholine (ACh) causes a rapid accumulation of this neurotransmitter within the synaptic cleft, at muscarinic and nicotinic receptors, causing intense postsynaptic cholinergic stimulation. The constant activation of nicotinic receptors generates involuntary skeletal muscle contractions followed by a complete depolarization-like block.[14] The accumulation of ACh in the CNS causes anxiety, disorientation, general convulsions, and coma.[13,14] The latter effects can ensue seconds after exposure to the intoxicating agent, evolving rapidly to respiratory arrest.[1] Hemodynamic collapse, accompanied by bradycardia, is another muscarinic action that precedes death.[15] The NA-induced ACh accumulation at muscarinic sites also augments the activity of various secretory glands, leading to excessive salivation, lacrimation, urination, diarrhea, and gastrointestinal discomfort. The smooth muscle ac-

Table 3. Specific Antidotal Treatment for Nerve Agent Intoxication as Recommended by the Israeli Defense Force Medical Corps[6,25]

Clinical Severity	Atropine	Scopolamine#	Pralidoxime Chloride**	Obidoxime
Mild*	2 mg intramuscularly every 20 min until full atropinization§ Children: 0.02 mg/kg	0.25 mg intramuscularly every 4–6 h	1–2 g intramuscularly (single dose) Children: 15–25 mg/kg intramuscularly	250 mg intramuscularly every 2 h (maximum of 3 doses) Children: < 2 yr: 62.5 mg intramuscularly every 2 h (total of 3 doses) 2–10 yr: 125 mg every 2 h (maximum of 3 doses) > 10 yr: as in adults
Moderate†	Repeat intravenous dose (2 mg) every 5–10 min until full atropinization Children: 2 mg or 0.02–0.1 mg/kg	0.25 mg intravenously repeated within 30 min, then every 4–6 h	1–2 g intravenously (single dose)	30-min intravenous infusion of 250 mg every 2 h (maximum of 3 doses; up to 2 g if clinically effective) Children: slow intravenous infusion, 250 mg every 2 h (maximum of 3 doses, additional 5 doses if clinically effective)
Severe‡	As in moderate conditions	As in moderate conditions; repeat doses if necessary	Same as for moderate conditions	Same as for moderate conditions

* Patient walks but suffers from miosis, blurred vision, lacrimation, salivation, chest discomfort, nausea, and vomiting and abdominal pain. † Patient is lying down, breathing is laborious with marked wheezing and bronchospasm, muscle fasciculation, and urinary and fecal incontinence. ‡ In addition to all of the manifestations mentioned for mild and moderate, patient is apneic.[25] § Characterized by the appearance of flushed and dry skin, increased heart rate, and reduced bronchoconstriction and bronchorrhea. Mild and moderately intoxicated patients must be atropinized for at least 24 h. Severely intoxicated patients should be kept fully atropinized for at least 48 h. Adults older than 60 yr should be given additional doses of atropine of only 1 mg each after the initial 2-mg dose. Mildly intoxicated children younger than 2 yr should be given atropine only after careful clinical evaluation and verification of the necessity for additional atropine, since they are more susceptible to atropine intoxication. # Not recommended for children. ** Repeated doses of pralidoxime at hourly intervals should be given in case of progressive worsening or persistent signs of toxicity. All drugs must be readministered as deemed clinically necessary. An integral part of the antidotal protocol consists of the administration of a benzodiazepine to reduce anxiety and resistance to mechanical ventilation or to control seizures (intravenously or intramuscularly, preferably 0.05–0.1 mg/kg midazolam or 0.2 mg/kg diazepam) in fractionated doses or until the desired effect is achieved.

tivity is exaggerated as well, resulting in increased peristalsis, bronchial constriction, and miosis.

Antidotal Treatment

The pharmacologic approach of choice for individuals already intoxicated by NA is the administration of muscarinic receptor antagonists with mainly peripheral (atropine) or central (benactyzine, scopolamine) activity, as well as oximes and anticonvulsants (table 3). Atropine is the "gold standard" therapeutic agent for NA intoxication. It blocks the muscarinic receptor overstimulation, thus aborting smooth muscle contraction, cardiac manifestations of toxicity, and hypersecretion of the glands. Symptoms like bronchoconstriction, nausea and vomiting, abdominal cramps, and diarrhea are attenuated. Atropine reduces parasympathetic overstimulation and the consequent risk of bradydysrhythmias induced by ACh accumulation. Atropine must be given in large amounts that may reach up to 50 mg in a 24-h period before signs of full muscarinic antagonism appear in the adult. The limited experience with NA casualties indicates that only cumulative doses of atropine as high as 10–20 mg in the first 2 or 3 h of treatment will provide an adequate control of the toxic symptoms.[16] Initially, a dosage of 2 mg for adults and 0.02 mg/kg for children should be administered, preferably intravenously. The full effect (flushed and dry skin, pupillary dilatation, increased heart rate, and cessation of bronchoconstriction and bronchorrhea) is achieved with larger doses.[16] Maintenance intravenous treatment is necessary for 2 to 3 days to completely abort the intoxication.[14] It is noteworthy that patients may manifest tolerance to normal doses of atropine when intoxication is severe.[17] Insofar as miosis can persist after NA exposure and since skeletal muscle paralysis is not affected by atropine, these two parameters are not suitable for monitoring the degree of atropinization. Experience has shown that individuals at risk of an NA attack may self-administer repeated injections of atropine, which could result in disorientation and tachyarrhythmia.[18] Hemorrhage or hypovolemia, diarrhea, vomiting, or prolonged controlled mechanical ventilation are additional factors which may exacerbate NA-induced mental disorientation and hemodynamic instability which can be further aggravated by inappropriate or excessive atropine treatment.[19]

The effect of atropine on NA-induced paralysis and muscle flaccidity is minimal because of its lack of action at nicotinic receptors. If the dysfunction of the nicotinic neuromuscular synapse is to be eliminated and respiratory muscle paralysis is to be terminated, an oxime such as pralidoxime chloride, HI6, or obidoxime chloride should be used.[20–22] These nucleophilic agents act as

chemical reactivators of AChE. They compete with the thermostable bond generated between NA and the AChE active site at the nicotinic receptor, allowing less deactivation by the NA and almost normal AChE activity.[23] Prompt administration of the oximes following intoxication is essential. The mentioned NA covalent binding to the active site of the AChE undergoes a rapid process of "aging," *i.e.*, the chemical bond between the NA and AChE becomes progressively resistant to deactivators, starting minutes from the initial exposure.[15] If this occurs, the same AChE can not be reactivated anymore and the physiologic activity at the site will be restored only by synthesis of new enzyme. This process occurs in different rates in tissues or plasma,[8] and the return to fully normal activity may last up to 6 weeks in untreated patients.[24] Contrarily, in RBCs, AChE deactivation following NA exposure persists throughout the life span of the RBC, unless reactivated (a RBC turnover of 1% per day).[8] There are many types of oximes among which those possessing the bis-quaternary chemical structure, *e.g.*, pralidoxime chloride (2-PAM) or obidoxime are the most potent AChE reactivators. The former is the oxime recommended by the USA armed forces[8] while the latter is the choice of the Israeli Defense Force Medical Corps.[6,25] The recommended doses of pralidoxime chloride and obidoxime are presented in table 3. The initial doses can be repeated as deemed clinically necessary. Mild transient hepatic damage can develop in the higher dose ranges.

The aging process is variable and related to the toxic agent. It should be remembered that the soman gas (GD) becomes irreversibly bound to AChE within only a few minutes after the exposure, underscoring the importance of the immediate administration of an oxime. In these cases, the use of the oxime HI6 might produce better enzymatic reactivation,[21] because of the better accessibility of this oxime to the active site of the AChE.[26]

The effect of NA on the CNS receptors must also be abrogated as soon as possible with high doses of anticonvulsant agents to limit brain damage and suffocation that may result from prolonged seizure activity. Scopolamine and benzodiazepines intravenously or IM can prevent such occurrences[13,14]: the former has a sedative action in addition to a central anticholinergic effect, while the latter halts and prevents convulsions, reduces anxiety, and facilitate mechanical ventilatory support (table 3).

Use of pyridostigmine bromide (PYR) can be an effective preventive measure against NA intoxication. It was approved as the drug of choice for pretreatment against NA by the USA army, UK, Canada, Europe, and Israeli Defense Forces.[25,27] This drug is prophylactically administered orally in a dose of 30 mg (one tablet) three times daily to a given population at risk of NA exposure as soon as the risk becomes a real danger. PYR is a carbamate whose protective effects stem from its ability to create a reversible rather than an irreversible chemical bond at the AChE active site (fig. 1). Exposure to NA soon after PYR administration leaves the active site of AChE largely shielded since it is already bound to PYR. With time, however, the PYR-AChE bond gradually dissipates, and if no longer exposed to the drug or NA, the physiologic activity of AChE is restored, resulting in the breakdown of excessive amounts of ACh. ACh concentrations in the synaptic cleft return to physiologic levels, enabling the reestablishment of normal neuromuscular transmission.[7] Also, PYR reversibly inhibits 20–40% of AChE in RBCs, forming a semistable carbamylated enzyme that leaves the enzyme intact despite exposure to NA. The PYR-enzyme complex would break later spontaneously to liberate a fully functional enzyme.[7,18] If PYR pretreatment is given alone, it affords only partial protection against the potential NA lethality. Thus, in cases of a later real exposure, the full complex of antidotal drugs should be rapidly administered as well.

Partial enzymatic blockade at the synaptic cleft produced by PYR carries with it some degree of accumulation of ACh, resulting in transient cholinomimetic nicotinic and muscarinic overstimulation. This clinical entity is called "Gulf syndrome" and is characterized by weakness, diarrhea, nausea, vomiting, hyperperistalsis, excessive salivation, difficulty in breathing, and CNS signs (*e.g.*, restlessness, dizziness, hallucination). Drugs such as benzodiazepines and mucolytics may be needed to counteract these untoward effects.[27] These are similar to, but much milder than, NA-induced clinical symptoms and should subside approximately 12 h after the cessation of PYR treatment when AChE activity returns to normal.[28] Furthermore, it must be borne in mind that although PYR, atropine, scopolamine, and the oximes[7,21,29] are efficacious in the prevention or treatment of NA intoxication, they also can depress the circulatory system.[21,30] For example, oxime-induced reduced cardiac output and blood pressure have been attributed to its autonomic ganglion blocking effect.[22] This sequence of events may be further complicated by arrhythmias and a poor circulatory state, as has been observed in humans[1] and animals[31] when exposed to the potent NA sarin, or if hypovolemic shock occurs as well. Finally, the presence of a low perfusion state caused by a severe conventional injury may further affect the subsequent atropine or oxime therapy. Because these agents are also given by intramuscular injection, they may be absorbed unpredictably and act inefficiently under such circumstances.[6]

Primary Care of the Medical Staff

The existing first aid protocols for patients intoxicated by NA stress careful and immediate (if possible within 2 to 3 min from the exposure) decontamination of the body with the purpose of terminating the exposure and

preventing secondary contamination of the medical staff. This can be accomplished by removal of the offending agents by physical means or by chemical neutralization. The use of copious amounts of water on the exposed body area was adopted in Israel[6] and is also recommended by the American Medical Research Institute of Chemical Defense.[8] This method was proven to be as effective as the Fuller's Earth, sodium hypochloride, Dutch Powder, and other compounds currently used by some European countries.[8] The most effective chemical neutralization is obtained by oxidative chlorination of the NA using a freshly prepared alkaline hypochlorite solution (0.5%). However, the use of this solution is expected to be of limited value in the traumatized and intoxicated individual as the solution is recommended for intact skin and soft tissues only and is contraindicated for eye, brain, and abdominal wounds.[8] The decontamination process should be completed in the field or at least outside the medical center. Residual NA contaminating even a single victim's clothing within the hospital may generate sublethal concentrations of NA, which may generate anxiety and disrupt regular work schedules because the hospital staff may be ordered to undergo decontamination themselves and then be unavailable to work for several hours or days.[32] Such secondary exposure of the medical staff to gas vapor has been described when first aid treatment was given inside closed rooms (*i.e.*, an emergency room).[33]

All personnel involved in administering acute care to NA-intoxicated patients must wear adequate protective gear: ordinary surgical masks and latex gloves do not afford adequate protection from the toxic vapors. Full protective gear consisting of a suitable gas mask and butyl rubber gloves do provide protection but at the cost of impaired vision and dexterity.[34] Nonlethal ocular signs and symptoms such as severe miosis, dim vision, and persistent rhinorrhea can compromise the physician's ability to function.[33] Intubation of the trachea may also fail under such conditions because of the physician's impairment of vision and the presence of other disturbances. Extra caution must, therefore, be exercised by the anesthetist and emergency care team to prevent physical contact-induced cross-contamination when called on to manage the airway or treat severely affected victims.

In-hospital Acute Medical Care

Synergistic Effects of Physical Trauma and Nerve Agent Intoxication. The presence of clinical signs of concomitant physical trauma and those of chemical intoxication implies a more severe prognosis because of two mechanisms: (1) NA reduce the cardiovascular and respiratory capabilities of the body to compensate for the already existing severe physical trauma; (2) Tissue lacerations of any kind are ports of entry for the NA. In-hospital prompt and correct diagnosis of the nature of the trauma is imperative since delaying specific treatment or misdiagnosis can be fatal.[35] Aggressive atropine administration and system-oriented supportive care aiming at maintaining normal respiration, controlling seizures, and stabilizing the cardiovascular conditions are essential for survival after concomitant injury. The severity of the intoxication and the efficacy of the initial treatment measures should be assessed by rapid clinical examinations using preestablished criteria based on maintenance of a patent airway, the hemodynamic conditions, respiratory function, and prevention of neurologic deterioration (table 4).

Lengthy routine spectrophotometric analysis of body fluids or measurement of AChE activity in RBCs would most likely be inapplicable. The detection of miosis (< 3 mm) was reported as being a simple and sensitive index for NA exposure in nonatropinized patients (as after the sarin catastrophe in Tokyo in 1995).[36] Details of mass casualty on-site triage and first-aid treatment of trauma are beyond the scope of this review: a comprehensive overview can be found elsewhere.[5] However, the importance of scrupulous examination for physical trauma in the presence of NA intoxication cannot be overemphasized. The initial care of the toxic-traumatized patient can be difficult because of misleading mixed signs of NA intoxication and severe trauma which can confound the clinical picture (table 5). It should be remembered that abdominal pain associated with nausea, active vomiting, or dehydration can be the result of NA intoxication or PYR pretreatment, but the same signs and symptoms could also signal perforation or obstruction of a viscous. As a rule of thumb, the primary assessment of these patients must be conducted in accordance with the Advanced Trauma Life Support (ATLS®) principles for victims of conventional multiple trauma. Simultaneously, signs of increased parasympathetic activity should be sought as well and treated with large amounts of atropine from the time the patient is attended onward.

Patients with combined trauma and NA intoxication may be suffering from severe hypovolemia for the abovementioned reasons. The primary strategy for maintaining blood pressure is ample but judicious fluid administration, including blood (whenever indicated and available). In case of severe cardiovascular collapse, inotropes and vasopressors should be used in titration until the desired clinical condition is achieved. The use of dopamine and or epinephrine in conjunction with fluid resuscitation may be preferable to norepinephrine. Besides their α-adrenergic agonist effects, the former have pronounced tachycardic actions, which may counteract the negative chronotropic effects generated by NA or PYR.

Neurologic Considerations

The level of consciousness in the victim may become severely impaired not only because of serious NA intox-

Table 4. Suggested Dos and Don'ts in Physically Injured and Nerve Agent–intoxicated Victims

Stage/Aim	Do	Don't	Recommendations
Hospital arrival	Verify previous decontamination Toxicologic assessment System-oriented assessment and care	Treat patients if you are not protected with special gear Use cardiodepressant or cholinomimetic drugs	Triage-guided decisions Follow ATLS® guidelines Maintain patent airway Full atropinization if indicated Prefer epinephrine or dopamine over norepinephrine
Diagnostic steps	Meticulous anamnesis (verify signs and symptoms of physical trauma and/or NA intoxication) Severe muscle weakness in children Assess adequacy of antidotal treatment	Use cardiodepressant or cholinomimetic drugs	Toxicologic opinion (PYR *vs.* NA *vs.* organophosphates) DD of respiratory distress (NA, volume overload, cardiac failure) DD of mydriasis (previous therapy, head injury) DD of cardiac problems (NA, previous therapy)
Airway control	Rapid-sequence ETT and 100% O_2 Clear airways secretions Sedation/anticonvulsants if required	Use succinylcholine Use LMA, ILMA, or Combitube	Prefer nasal intubation Prefer rocuronium for ETT[62] High-pressure ventilation + PEEP
Acute care	Vigorous NA antidotal therapy Sedation/anticonvulsants if necessary Correct heart conduction abnormalities Bladder catheterization Intragastric tube insertion (after ETT)	Give cardiodepressant or cholinomimetic drugs	Meperidine (possibly with ketamine) for pain control Continuous airway toilette Fluids, dopamine or epinephrine Exclude/treat coagulopathy
Anesthesia	Inhalation (volatile) general anesthesia Possible peripheral nerve block Muscle relaxants titrated and monitored	Administer thoracic/high lumbar epidural or spinal anesthesia Apply conscious sedation Use cardiodepressant drugs	Etomidate or ketamine (for induction), meperidine (analgesia), pancuronium bromide, bupivacaine (RA or LA, with minimal sedation)*
Postoperative care	Continuous, vigorous NA antidotal therapy Sedation/hypnosis if required	Use neostigmine Extubate in presence of cholinergic overstimulation	Expect prolonged ventilation Meperidine (possibly with ketamine) for analgesia Continuous airway toilette
Pediatric care	Warming is essential Anticipate the need for large doses of atropine as NA antidotal therapy Follow adult resuscitation measures	Ignore intubation difficulty and rate-dependent cardiac output	CNS depression and hypotonia characterize pediatric intoxication Have a pediatrician available

* Since nerve agents (NA) depress the respiratory center, large amounts of sedatives are not recommended in this setting.

ATLS = Advanced Trauma Life Support; PYR = pyridostigmine bromide; DD = differential diagnosis; ETT = endotracheal intubation; LMA = laryngeal mask airway; ILMA = intubating laryngeal mask airway; PEEP = positive end-expiratory pressure; RA = regional anesthesia; LA = local anesthesia; CNS = central nervous system.

ication but also because of hypovolemic shock (*e.g.*, during internal bleeding). A decreased level of consciousness, together with difficult airway and cardiovascular instability, may aggravate the patients' conditions and complicate initial management. Obtundation and loss of consciousness can also result from earlier convulsions or large doses of benzodiazepines (table 2). It must be emphasized that the primary cause for the loss of consciousness may be a conventional head injury. If increased intracranial pressure is suspected, intravenous administration of lidocaine (1.5 mg/kg) and sedation with benzodiazepines (*e.g.*, midazolam 0.1 mg/kg) with or without the addition of small doses of opioids (*e.g.*, fentanyl 1 μg/kg) should take place before prompt laryngoscopy and intubation. In these cases, monitoring size and light reaction of the pupils may not be sufficient to rule out an ongoing intracranial pathology. Radiologic imaging or intracranial pressure monitoring would be appropriate, while at the same time, information on the mechanism of injury and initial treatment could help in accurately making a diagnosis. It is possible, however, that some of these measures would be unobtainable under the given chaotic circumstances. Finally, since the cholinergic receptors are spread throughout the CNS, poisoning by NA may also disrupt noncholinergic CNS neurotransmission in various neural sites,[37] producing a variety of neurologic signs, among them anxiety, emotional instability, and delirium (table 5).[38] These neurologic signs can lead to confusion as to what is the source of these disturbances (*i.e.*, late sequelae of the NA intox-

Table 5. Differential Diagnosis of Multiple Trauma–related and Nerve Agent Intoxication–related Clinical Signs

Clinical Finding	Cause
Pupil > 3 mm, not reactive to light	Pain
	Head injury (brain concussion/damage)
	Severe hypoperfusion
	Atropine/epinephrine overdose
Miosis, minimally reactive to light	Opioid overdose
	Intracranial hemorrhage
	NA intoxication
	PYR treatment
Secretory conditions	Severe allergic reaction/asthma
	Upper respiratory infection
	NA intoxication
	PYR treatment
Tachycardia	Anxiety
	Pain
	Ketamine administration
	Hypovolemia/hemorrhage
	Hypoxia
	Optimal atropinization
	Low dose/initial phase of NA intoxication
Bradycardia	Opioid overdose
	Increased intracranial pressure
	Severe hypovolemia/hemorrhage
	Chest blunt trauma
	NA intoxication
	PYR treatment
Low perfusion state	Hypovolemia/hemorrhage
	Hypothermia
	Myocardial event
	Pulmonary fat embolism
	NA intoxication
	PYR treatment
Dyspnea, airway congestion/secretions	Congestive heart failure/pulmonary edema
	Myocardial event
	Hypertensive rebound/crisis
	Fluid/blood overload
	Asthma attack
	Pneumonitis
	Post–gastric reflux/aspiration
	NA intoxication
	PYR treatment
Unconsciousness/coma	Head trauma
	Brain injury
	Opioid/benzodiazepine overdose
	Post–ictal state
	Severe NA intoxication
Muscle weakness	Opioid/benzodiazepine overdose
	Partial reversal/rebound of relaxation
	Head trauma/brain injury
	Cerebral vascular accident
	PYR treatment
Limb restlessness	Anxiety
	Signs of shortness of breath/air/hypoxia
	NA intoxication
	PYR treatment
Urinary incontinence	Normal in neonates, infants, and toddlers
	Bladder overload
	Diuretic usage
	NA intoxication
	PYR treatment
Abnormal coagulation indexes	Massive blood transfusion
	Hypothermia
	Anticoagulation therapy
	NA intoxication

NA = nerve agent; PYR = pyridostigmine bromide.

ication or other etiologies). These patients, nevertheless, require proper symptomatic care and sedation (*e.g.*, midazolam, 0.05–0.1 mg/kg) if necessary.

Respiratory Failure: General

Respiratory failure following exposure to NA inevitably leads to death if not immediately treated. NA cause respiratory insufficiency by virtue of their depressive action on the central respiratory center[39] as well as at the neuromuscular junction and the airways. Irritation of both the upper and lower airways, their obstruction by bronchorrhea, toxic pulmonary edema, and severe bronchoconstriction, are the effects of severe parasympathetic overstimulation and subsequently increase airway resistance. These conditions would adversely affect pulmonary gas exchange, leading to hypoxic and hypercarbic respiratory failure.

Prehospital Respiratory Failure

Outside the hospital, a complete physical examination of the respiratory system may not be performed because of the imperative need for personal protection. Hence respiratory assessment would be limited to observation of the patient's color, the use of accessory muscles, and the respiratory rate and pattern (visually detected abnormal movement of the thorax and abdomen). A modified bag-valve-mask device or a portable ventilator would probably be used in the contaminated zone. If a self-inflating bag is used, it should be provided with a special filter, like the standard NATO filtration canister, which protects the inlet port of the resuscitation bag from further contamination.[40] When portable ventilators are used at the disaster site or immediately following decontamination, continuous oxygen supply may pose a problem, particularly if it is used as a driving gas for the ventilator. Using one of the portable ventilators, such as the CompPac® or the newer version CompPac 200® (Pneupac Ltd., Luton, UK), which were designed for use in difficult environments, are capable of delivering synchronized intermittent mandatory ventilation. Because these ventilators are capable of filtering the contaminated air and using it as a driving gas, their use could be of advantage. This series of flow-generated portable ventilators is electronically or pneumatically powered and are thus suitable for emergency ventilation in a contaminated area, especially since they are also equipped with a battery supply that enables a 4-h uninterrupted function.[41]

We have used within and outside the hospital several types of air–oxygen-powered automatic and single-patient use resuscitators, which provide constant flow and pressure-cycled ventilatory support in either a mandatory or an intermittent mode. A suitable single use ventilator is the RespirTech PRO® (VORTAN® Medical Technology 1 Inc., Sacramento, CA). It is a constant flow, time-cycled, pressure-limited device, which contains an

exhalation valve that opens at predetermined peak inspiratory pressure and closes at preadjusted positive end-expiratory pressure. A pop-off valve adds an element of safety to this device. A relatively cheap, reusable ventilator is the pressure-cycled OXYLATOR® EM-100 (CPR Medical Devices Inc., Toronto, Canada). Originally designated for short-term patient transportation, this model can be used for long periods of time. It is made of hard acetate, delivers minute volumes of 12–16 l/min in auto mode and is autoadjustable to lung capacity with pressure relief of 20 cm H_2O. Positive end-expiratory pressure (PEEP) is maintained at 2–4 cm H_2O. A second resuscitator of the same series is the pressure-limited OXYLATOR FR-300. Minute volume ranges between 10–12 l/min and the maximal flow rate is 30 l/min. The pressure relief in this latter ventilator ranges between 25–50 cm H_2O. It is also provided with an inhalator port with maximal flow capability of 15 l/min. Both devices are light (500 g and 180 g, respectively), have an oxygen flush button, and are equipped with a standard oxygen DISS, ISO inlet connection. These personal ventilatory assist devices allow air entrainment but do not filter contaminated air, which eventually becomes contaminated. These simple and relatively cheap devices may provide an initial solution for multiple casualties requiring ventilatory assistance simultaneously.

In-hospital Respiratory Failure

Preventing or treating respiratory insufficiency is the most crucial step toward salvaging the intoxicated and traumatized patient. Nevertheless, it is unwise to withhold antidotal treatment until proper oxygenation is assured and ventilation is satisfactorily controlled. Traumatic cervical injury needs to be excluded in every patient before airway manipulation by the attending physician. Benzodiazepines would be the drugs of choice and perhaps the only necessary ones to sedate these patients before intubation in the given circumstances. A useful adjunct for airway protection can be the oro- or nasopharyngeal artificial airway, which can be inserted before tracheal intubation and facilitate secretion removal. The patient is then placed in the lateral decubitus position according to the recommendations of the International Liaison Committee on Life Support.[42] The safest mode of airway protection would be tracheal intubation, but some concerns may arise from a possible low success rate when performed by physicians called on in a mass casualty scenario who are not familiar with this procedure. The laryngeal mask airway was suggested as an acceptable solution to facilitate a rapid and easy ventilatory access, even by physicians with limited experience in airway management[43,44] and wearing protective gear.[45] However, due to poor lung compliance, increased secretions, and bronchospasm, effective ventilation using the laryngeal mask airway in this scenario is questionable. The use of the Combitube (Combitube SA®, Kendall Sheridan®, Mansfield, MA), an esophageal tracheal airway, is also not a good choice in the presence of massive bronchorrhea because suction of the airways is not possible with this device. Patients should be considered as having a "full stomach," and neither the Combitube nor a laryngeal mask airway will protect against aspiration. Awake intubation or rapid sequence induction using the Sellick maneuver are the only safe techniques of intubation in such patients. In the presence of severe respiratory failure, pulmonary edema, copious secretions, or marked bronchial constriction, high blood oxygen saturation may not be achieved before intubation, with the associated possible cardiovascular and cerebral implications. Importantly, the presence of hypoxia in the fully atropinized patient can cause ventricular fibrillation, paradoxical bradycardia, and atrioventricular dissociation if intubation is delayed.

Nerve agent casualties may also exhibit wheezing, prolonged expiration, stridor (as a sign of laryngeal edema or spasm), and moist rales. These reflect airway reaction to the chemicals, *i.e.*, severe bronchial constriction or excessive amounts of secretions. For instance, soman was reported to affect lung mechanics, causing an increase in airway resistance and a decrease in lung compliance associated with pulmonary edema.[6] Nevertheless, in the combined casualty these signs could also indicate fluid overload resulting from earlier fluid infusions administered to treat hemorrhage or hemodynamic instability. It is necessary to regularly aspirate the airways, preferably by sterile means, starting soon after intubation. Repetitive verification that the endotracheal tube is both secured and correctly positioned is important because excessive perspiration and overwhelming amounts of oral and airway secretions might dislodge it. For this reason, nasal intubation might be preferred to the oral route. PYR alone can also cause a dose-dependent increase in airway resistance because of the heightened muscarinic activity that causes bronchial smooth muscle contraction. AChE inhibition produced by PYR and the resulting ACh excess could also aggravate airway irritation in patients with hyperreactive airway disease.[46]

Within the hospital and throughout the acute care and perioperative period, continuous vigilance is required to assure airway patency and adequacy of ventilation. Respiratory support should consist of pressure-controlled mandatory ventilation mode using 100% oxygen and PEEP that would best deliver adequate minute volume in these patients. Close monitoring for the early appearance of signs of barotrauma (such as sudden elevation of airway pressure or a decrease in systemic blood pressure) is essential, but perhaps rarely achievable in the anticipated chaotic conditions. It should be noted that the use of atropine, while antagonizing the cholinergic overstimulation and reducing secretions, may not halt the severe bronchoconstriction. In these cases, the use of β-agonists [*e.g.*, aerosolized albuterol (2.5 mg in 3-ml

saline) and ipratropium bromide inhalation (0.5 mg similarly prepared)] combined with steroids (intravenous methylprednisolone 125 mg three times daily) may be of some added value.[47] These pharmacologic agents and provision of mechanical support are probably the only way to achieve a rapid clearance of the noncardiogenic airway–pulmonary congestion–edema.[48]

Cardiovascular Considerations

Exposure to AChE inhibitors may cause cardiac abnormalities which themselves can lead to fatal outcome. These include rate, rhythm, and conduction disturbances, which may be especially severe in the presence of underlying cardiac disease, acidosis, or hypoxia.[49] Soon after intoxication, in the presence of sublethal doses of NA, a brief period (minutes) of cardiac overstimulation resulting in hypertension and sinus tachycardia may occur and is attributable to an augmented nicotinic receptor stimulation by NA.[50] This effect may derive from ACh-induced stimulation of the adrenal medulla and sympathetic ganglia to release catecholamines into the circulation and to activate postganglionic sympathetic nerve endings.[51] The second phase of cardiac interference of the NA may last a few hours and is characterized by severe cardiac depression manifested as bradycardia and hypotension caused by parasympathetic overstimulation of the muscarinic receptors. In this phase, ischemic ST-T changes may appear as well as atrioventricular (AV) conduction disturbances, which together with bradycardia may eventually produce malignant ventricular arrhythmias. Electrocardiographic appearance of prolonged Q-Tc denotes a poor prognosis.[52] These disturbances were attributed to NA-induced coronary vasospasm, as was reported after sarin intoxication,[53] or to direct myocardial toxic effects, as observed in rats exposed to sarin or soman.[31] Standard noninvasive hemodynamic assessment may not accurately define the nature of the cardiac impairment and the intravascular volume status. This is especially true in the presence of sublethal doses of NA, which may cause temporary elevations of blood pressure and cardiac output during the period of augmented sympathetic discharge.[50] It must be recognized that hypotension, for instance, may be caused by intravascular volume depletion as a result of vomiting, diarrhea, or excessive secretions, to trauma-induced internal bleeding, or to a reduction in cardiac output due to negative inotropic and chronotropic effects of the NA.[1] Tachycardia could be caused by hypoxia, hypovolemia, anxiety, inadequate analgesia, or the effect of full atropinization—all causes that could also be NA-independent. The cholinomimetic activity of the NA can induce severe intractable bradycardia, which can be confused with increased intracranial pressure after a head injury. In such circumstances, invasive hemodynamic monitoring would be necessary to determine the correct pathophysiologic cause. However, in scenarios of mass casualties, the shortage of medical personnel and equipment would severely limit the possibilities of inserting pulmonary artery catheters and transesophageal echocardiographic probes in all the victims who need them.

Patients will probably require the insertion of an indwelling urinary catheter (after their airways and cardiac conditions have been satisfactorily stabilized) due to the effects of the toxic agents or the antidotes on the bladder sphincters. An intragastric tube would also be required in most patients because of the severe nausea and vomiting that frequently accompany NA intoxication and because of the expected prolonged ventilation.

Anesthesia and Perioperative Care

Medications such as atropine, glycopyrrolate and scopolamine are used in anesthesia primarily for the reduction of secretions and minimization of vagal response, particularly in infants and neonates. These drugs are the treatment of choice for NA intoxication. PYR-induced cholinomimetic activity will also increase the parasympathetic activity and, therefore, large doses of muscarinic receptor antagonists should be used preoperatively to increase heart rate or reduce salivation or bronchial secretions in patients under the effects of PYR.[28] A report based on PYR-treated soldiers during the Gulf War stressed the need for atropine premedication to combat copious upper airway secretions.[54] Importantly, unlike organophosphates or NA, carbamates (*e.g.*, PYR) penetrate the blood brain barrier poorly, and their main activity is peripheral. Thus, while significant interference of PYR with the centrally acting anesthetics is not anticipated, other drugs, *e.g.*, scopolamine, that are still necessary to counteract the CNS effects of NA, may prolong sedation and disorientation in patients under general anesthesia and could act additively with PYR on peripheral receptors.

The safest technique of anesthesia in the intoxicated and physically traumatized patient is likely to be general anesthesia, whereby surgery is accomplished while airways and oxygenation are secured, the hemodynamic conditions are closely monitored and the CNS is protected. Nevertheless, it is very likely that there will be pharmacologic interactions between NA, their antagonists, and anesthetic drugs. Sodium thiopental might be utilized in the patient requiring intubation. The effect of sodium thiopental in casualties with preexisting asthma in the presence of cholinergic stimulation, might, however, lead to severe bronchoconstriction. Hemodynamically, the barbiturate-induced direct myocardial depression and peripheral vasodilation may be more pronounced in the presence of PYR or NA because of their vagotonic activity. These cumulative negative inotropic and chronotropic effects may be hazardous, especially in the presence of severe hypovolemia produced by trauma and in the presence of excessive perspiration,

diarrhea, or heat overload.[55] These effects mandate cautious use of this induction agent, whereas fluid infusion and vasoactive drugs may be extremely useful.

Ketamine is commonly used to induce anesthesia and analgesia in hemodynamically compromised and debilitated patients. Both ketamine and PYR can increase upper airway secretions, thereby increasing the potentials of severe dyspnea or sense of "suffocation" when used concomitantly. Atropine, and perhaps even better, glycopyrrolate, can attenuate these effects. Ketamine also causes bronchodilation, which might be beneficial in PYR-treated or NA-intoxicated patients, especially for patients with asthma or chronic obstructive pulmonary disease. In addition, ketamine-induced sympathomimetic activity can antagonize, even if only minimally, the overwhelming parasympathetic cardiac effects of the various NA-related drugs. Nevertheless, a recent experimental study in swine demonstrated a potentially dangerous reaction to ketamine (prolonged apnea and respiratory distress) when animals were exposed to sulfur mustard.[39] These results still remain unexplained, but suggest cautious use of ketamine in the presence of intoxication caused by a combination of chemical weapons, especially if mustard gas is involved.

Hemodynamic stability would best be achieved during induction of anesthesia with drugs such as etomidate that have minimal effects on cardiovascular regulation. It may be a relatively safer induction agent than a barbiturate for traumatized patients previously treated with PYR or intoxicated with NA. Propofol, an alternative induction agent, can cause myocardial depression and vasodilation even in patients with no signs of hypovolemia. It also temporarily depresses respiration so that unless its dose-dependent effect is carefully titrated, further cardiovascular instability or respiratory depression may ensue. Therefore, propofol as well as sodium thiopental should be employed with extreme caution in mixed toxic and trauma casualties.

Volatile anesthetics are potential bronchodilators and relax skeletal muscle to various degrees by means other than the AChE-ACh mechanism of action. Compared with intravenous anesthetics, their use might be advantageous due to their muscle-relaxing effect, sparing the need for additional use of muscle relaxants. This also avoids later interaction of neostigmine with NA or their antagonists. Interestingly, volatile anesthetics were shown to induce a false-positive reading in chemical agent-monitoring devices used by the emergency response teams and armed forces to trace chemical warfare agents and to find chemical weapon-contaminated shrapnel.[56] False-positive readings might result in prolonged and unnecessary exploration for shrapnel in certain patients. This will delay life-saving procedures, not only because of the time consumed, but also because of the difficulties in carrying out vital procedures while wearing protective gear.[56] Thus, knowing the limitations of such monitoring devices minimizes unnecessary effort and time and helps to limit confusion in the mass casualty scenario.

Opioids are an essential component in every form of general anesthesia. They do not directly affect cholinergic receptors and would not be expected to act in a reciprocal manner with NA and PYR-associated AChE pharmacology. There are no data assessing the use of opioids in the NA-intoxicated patient. Morphine may induce bronchial constriction (due to its histamine-releasing potential), which could exacerbate bronchoconstriction that had already been produced by PYR or NA. Such patients would become increasingly dyspneic and would more likely require assisted ventilation, or, if they were being ventilated, they might require increased peak ventilatory pressure with the attendant risk of barotrauma. Morphine can also cause hypotension by the same histamine release mechanism. Subsequent venodilation[57] could further exacerbate the hemodynamic instability of such patients. Furthermore, both fentanyl and morphine are potentially vagotonic, a characteristic which may lead to more pronounced bradycardia,[57] especially in chronic β-blocking users or in the presence of a slow heart rate due to the cholinergic effect of PYR or NA. Here, the use of meperidine (PRN, intravenous 0.25 mg/kg) as an analgesic may be preferable. Meperidine lacks histamine-releasing effects and tends to cause tachycardia.[57] High doses of opioids, especially fentanyl, alfentanyl, and remifentanyl, may cause skeletal muscle rigidity after their intravenous administration.[58] This may further impair the patient's respiratory mechanics in addition to the existing bronchial secretions or spasm. A prolonged activity of the otherwise normally short-acting drug, remifentanyl, should be anticipated as well because both NA and PYR inactivate the nonspecific tissue esterases that participate in the rapid hydrolysis of this opioid.[58]

All muscle relaxants block the nicotinic receptor's activity at the neuromuscular junction. Succinylcholine is a unique analogue of ACh since its structure is that of a di-acetylcholine. The excessive ligands that accumulate bind to the ACh receptor at the neuromuscular junction, resulting in prolonged depolarization followed by muscle paralysis. This neuropharmacologic mechanism is similar to that of the NA-induced AChE inhibition except for the fact that the effect of succinylcholine is reversible within minutes. Thus, in the presence of pretreatment with PYR or under the effects of NA poisoning, the amount of succinylcholine necessary to produce sufficient muscle relaxation for tracheal intubation should be reduced significantly.[28,59,60] PYR, and NA-induced inhibition of plasma cholinesterase activity further limits succinylcholine degradation. Nevertheless, the duration of the relaxation was not reported to have changed when Gulf War soldiers were given the drug while they were experiencing the effect of PYR.[54] It is recom-

mended, however, to abstain from using succinylcholine in these patients. Under such circumstances, rocuronium for intubation, using doses slightly above the normal intubation dosage (0.6 mg/kg) may be preferred[61] because of its mild vagolytic effect and lack of AChE-dependent metabolism (table 4).[62]

Neuromuscular blockade by nondepolarizing muscle relaxants in the presence of pretreatment with PYR theoretically should be attenuated, and dose adjustments may be required. In the presence of inhibition of AChE, larger than usual amounts of ACh at the synaptic cleft compete with the nondepolarizing muscle relaxants at the postsynaptic cleft. While there are no controlled data regarding the effects of nondepolarizing agents during NA intoxication, pancuronium bromide might be a preferred choice due to its associated positive chronotropic effects. When alcuronium was used in an isolated human arm, no change in the degree of muscle paralysis was observed in a subject who had been given PYR previously.[63] In addition, soldiers stationed in the Gulf War area who were pretreated with PYR did not require larger than the anticipated doses of vecuronium to maintain muscle paralysis.[54] Nevertheless, careful monitoring of neuromuscular blockade would be especially prudent when subsequent doses of relaxants are required. If a typical train-of-four response presents a fade, additional divided doses of relaxants must be given cautiously to prevent prolonged muscle paralysis.

The practice of using neostigmine for the reversal of neuromuscular blockade in organophosphate-intoxicated or PYR-treated patients has been discussed but recommendations are still equivocal.[64] It was suggested that blood transfusion to organophosphate-intoxicated patients may partly replenish the reduced stores of AChE and therefore neostigmine administration would be warranted after the use of nondepolarizing muscle relaxants.[65] Nevertheless, because of the excessive airway secretions that accompany NA intoxication or the administration of PYR, it would be wise to limit the use of neostigmine since it would aggravate the secretion load. This highlights the need to exercise extra caution when using muscle relaxants intraoperatively. If necessary, muscle relaxant administration should be titrated, based on both nerve stimulator response and on the return of normal muscle force, thus minimizing the need for neostigmine and the resultant augmented muscarinic hyperstimulation. Also, PYR was shown to act similarly to neostigmine.[66] Both compounds block the AChE activity—albeit with a different duration and potency—leading to high ACh availability and thus restoring normal neuromuscular activity. It is not yet established whether PYR-pretreatment requires larger than normal doses of neostigmine to overcome the paralytic effect of the muscle relaxant in a reliable and durable fashion.

Postoperative Care

Prolonged muscle weakness associated with breathing difficulties are the most likely and hazardous postoperative complications. Residual neuromuscular blockade and NA-induced muscle paralysis can also affect the muscles of the tongue and pharynx. This can lead to prolonged postoperative upper airway obstruction.[67] Delayed episodes of asphyxia caused by bilateral recurrent laryngeal nerve paralysis have been reported following pesticide organophosphate poisoning both in nonsurgical patients[68] and postoperatively.[38] For this reason, at the completion of surgery, patients should be fully awake, clear of secretions, and able to maintain their upper airway reflexes. Victims of combined trauma and NA toxicity should breathe adequately without difficulty before being extubated. It should be remembered that delayed muscle weakness can follow the initial cholinergic crisis even as late as 4 days after the acute exposure to AChE inhibitors. This type of paralysis barely responds to the antidotal treatment used for the acute intoxication.[69] If this yet not completely understood phenomenon occurs, supportive respiration should be delivered in an intensive care setting for as long as necessary (often for several days).

Another possible postoperative musculoskeletal complication is severe myonecrosis produced by the excessive accumulation of ACh in the synaptic cleft causing calcium flux into the skeletal muscle during the NA poisoning.[70,71] Calcium overload causes myocyte death. The subsequent development of rhabdomyolysis could cause renal damage. Close monitoring (if available) of serum creatine kinase and potassium, especially in the combined trauma patient, is advised to prevent subsequent myoglobinuric renal failure and severe dysrhythmias. Adequate hydration, forced diuresis, and urine alkalinization are the cornerstone of treatment as soon as the color of the urine turns reddish without an apparent explanation.

Any eventual necessity requiring prolonged postoperative ventilation, even for only a few post-surgical patients, could deplete the number of available ventilators, which will also be required for patients intoxicated by NA alone. The use of continuous positive airway pressure (CPAP) ventilation was described as an optimal method for ventilatory support in patients who suffered from organophosphate intoxication.[72] Nevertheless, it is questionable if patients suffering from pulmonary edema due to NA intoxication and who have had a thoracic or abdominal surgical procedure can maintain consciousness and remain cooperative while they are being treated with a CPAP mask. The use of this method of respiratory support may also be inappropriate in the presence of a full stomach or bowel paralysis. Availability of gas powered automatic resuscitators (see section on prehospital respiratory failure) could solve a large part of this logistic problem.

Finally, CNS involvement as a result of NA poisoning[37] may also produce a variety of neurologic signs (*e.g.*, anxiety, delirium[38]), which require extra caution before extubating the patient and discharge from the PACU or ICU.

In the immediate postoperative period, there may be a sudden appearance of cardiovascular instability and ventricular arrhythmias including the "torsade de point" type of ventricular tachycardia. The period of vulnerability, causing significant prolongation of the Q-T interval,[73] may last up to 15 days after the initial exposure to NA. Close monitoring and prevention of hypothermia and hypoxia are advisable in severely intoxicated casualties, especially after surgery with inhalation anesthetics (known to be capable of interfering with the myocardial conduction system and also prolonging the Q-Tc interval). Repeated electrocardiographic tracings would be mandatory before the patient is discharged to the general surgical ward[74] and after normokalemia and adequate oygenation have been established. Asymptomatic prolongation of the Q-Tc should not be treated,[74] but a QTc of greater than 580 ms denotes a high risk for sudden cardiac arrest.[73] Emergency treatment of "torsade de point" includes, in addition to cardioversion when indicated, the administration of additional doses of atropine to abrogate the toxic effects of the NA on the myocardium, as well as intravenous magnesium sulfate (1 to 2 g) or isoproterenol (2–8 μg/min).[42] Magnesium is, however, contraindicated in the presence of accompanying AV block or bradycardia, and as with isoproterenol which requires titration, could be difficult to administer in the scenario of multi-casualty events when automatic syringes are not available. Temporary cardiac pacing is an additional option but it is doubtful whether it would be practical for numerous patients in this scenario.[74]

No data exist in humans, but minor and probably non life-threatening changes in coagulation parameters (thrombin and prothrombin time) can occur following exposure to NA as was demonstrated experimentally in rabbits (table 5).[75] These should be differentiated from postoperative coagulopathy, *i.e.*, those that are caused by massive blood transfusion or hypothermia and treated according to clinical manifestations and laboratory tests.

Another important issue is the monitoring of body temperature in the perioperative period for various reasons. On-site excessive heat loss, prolonged exposure of injured body areas, cold-water showers, and loss of body heat during surgery are causes of hypothermia which need expeditious correction.

When vapor inhalation is the primary route of exposure, peak toxic effects of NA occur within minutes and largely resolve after 24 h. In contrast, a significant delay of symptoms that reach their peak only after several hours can occur after dermal exposure, especially after VX poisoning.[13] Hence, knowledge of the route of exposure will aid in planning the time of discharge from the postanesthesia recovery unit.

Regional Anesthesia

The use of techniques for regional anesthesia in cases of combined conventional injuries and NA intoxication deserves some consideration. While the patient's cooperation is essential if surgery is to be undertaken under regional anesthesia, NA-intoxicated patients may well be disoriented (either because of the intoxication itself or due to the centrally acting antidotes or sedatives). The application of regional anesthesia is time consuming, and time may be sorely lacking under these chaotic conditions. However, the use of an isolated nerve block (mainly for orthopedic procedures) may have an advantage over general anesthesia, especially in the patient with a full stomach. In addition, unlike other regional techniques, peripheral nerve blocks are not expected to exacerbate hemodynamic instability secondary to an already dysfunctional autonomic nervous system. If regional techniques are applied, care should be taken to limit combination of the sympatholytic effect with the parasympathetic hyperactivity generated by NA. Hence, the use of neuroaxial blocks (*e.g.*, thoracic epidural, high lumbar epidural or spinal block, all of which involve a sympathetic blockade of a poorly defined extent) could be hazardous. If used, they should be based on local anesthetics only, without the addition of opioids, to minimize possible immediate or late (depending on the lipophilicity of the opioid) respiratory depression. Whatever choice is made, proper ventilation and oxygenation of the patient should be continuously maintained (and monitored) during the surgical procedure. Amides may be preferable to the ester type of local anesthetics for use in regional blocks, since the latter are degraded by plasma cholinesterase, an enzyme that is inhibited by the NA or its PYR antagonists. In contrast, ester type local anesthetic may be a better choice if prolonged regional anesthesia is indicated.

In view of the anticipated coagulopathy that can accompany NA intoxication,[75] the use of a neuroaxial block must be a second choice of anesthesia and carefully weighed against the possible complications, such as neuroaxial hemorrhage. Conscious sedation will probably be unacceptable as a reliable technique under the given circumstances and in the described patients.

Pain Control

Because there are no data on the optimal combinations of various analgesics to be used in these patients, any attempt to delineate the most fitting and safe analgesic regimen should take the following aspects into consideration:

1. Pain control must be given as soon as possible by any reliable route.
2. The use of meperidine, which also has muscarinic

antagonistic properties, may aggravate an already existing NA-induced respiratory depression but enables continuous treatment and better patient cooperation.
3. In chaotic situations, the administration of any analgesic might not be accompanied by the normal means of patient monitoring (*i.e.*, respiratory and oxygen saturation monitoring or medical staff attendance). Therefore, small repeated doses are preferred to prevent exacerbation of the respiratory depression secondary to NA intoxication.
4. Patient-controlled analgesic may be inappropriate for NA-intoxicated patients since they are not expected to be lucid and cooperative.
5. If intravenous patient-controlled analgesia is an option, ketamine in subanesthetic doses (0.25 mg/kg bolus followed by 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ infusion) may be an alternative or an adjuvant to opioids. Use of ketamine[76] is not associated with cardiorespiratory depression and can produce bronchodilation.
6. If continuous epidural analgesia is used, it should consist of the administration of low doses of amide local anesthetics without opioids, *e.g.*, bupivacaine 0.125%, 6–8 ml/h by a lumbar approach. Depending on the relative location of the injury, adequate analgesia may not be provided by the epidural alone and intravenous supplementation may be necessary.

The Nerve Agent-Intoxicated-Physically Traumatized Child

The ATLS® and the TOXALS® guidelines[1] are the only available and acceptable resuscitation methods to be followed when a potentially lethal penetrating or blunt trauma occurs in the intoxicated-traumatized child.

Resuscitation of NA-intoxicated children is a greater challenge than with adults because of their smaller physical size and the difficulties in managing their airways or in placing intravenous cannulae. Furthermore, the protective clothing and devices worn by the care providers can impede rapid establishment of patent airway, breathing, and circulatory assistance. Active participation of a pediatrician in the special intensive care team is, therefore, highly recommended. It should be noted, however, that specific knowledge of how best to treat a child exposed to NA is still a matter of debate. The current therapeutic strategy is largely based on an extrapolation from reports of children inadvertently intoxicated with various pesticides having AChE inhibitory properties.[17] The American Academy of Pediatrics recently summarized special aspects of NA intoxication in children.[77] According to this report, it should be expected that children would be more susceptible to the toxic effects of NA. The higher minute ventilation in children would lead to a greater exposure to aerosolized NA than in adults. In addition, the high vapor density of gases such as sarin places the highest concentration close to the ground, in the breathing zone of children. Another factor is the high grade of permeability of the skin of newborns and children in conjunction with a larger surface-to-mass ratio, possibly resulting in a greater exposure to transdermally absorbable toxic agents, such as VX.

Additional issues need to be considered when treating intoxicated-traumatized children: due to their relatively larger body surface area, children tend to lose heat quickly when showered during decontamination of the skin. Pronounced hypothermia aggravates any already existing coagulopathy, and together with loss of consciousness and acidosis, lead to rapid demise.[77]

The diagnosis of NA exposure in children may be more difficult to establish than in adults (tables 2, 5). In the pediatric population, the predominant clinical manifestations are CNS depression and severe hypotonia, rather than the classic muscarinic overstimulation observed in adults.[78] Indeed, bradycardia and muscle fasciculation appeared in only one-fifth of the children exposed to organophosphate poisoning.[17,78] Other signs such as miosis, diarrhea, and salivation may also be less frequent than in adults.[78] Importantly, excessive salivation, fatigue, and incontinence are not necessarily pathologic for certain ages of the pediatric population, thus stressing the importance of meticulous anamnesis and correct diagnosis to exclude possibilities other than NA intoxication.

The incidence of centrally induced general convulsions following organophosphate intoxication is greater in children than in adults (table 5).[17] These result from hypoxia that develops more rapidly in children because of respiratory muscle weakness. Doses of atropine that would be expected to be effective in antagonizing the effects of the intoxication in children are relatively higher than the dose of 0.02 mg/kg commonly used during resuscitation in pediatric patients.[79] Doses of atropine as large as 0.05 mg/kg were found to be only minimally effective, and doses up to 0.1 mg/kg will sometimes be needed (table 3).[17] It is recommended that atropine be administered in titration until a complete resolution of the cholinergic crisis is obtained. Atropine should not be stopped in the presence of tachycardia since, in contrast to adults, repeated boluses do not cause cardiac arrhythmias in children.[79] Other drugs commonly used to abrogate the toxicity of NA in children include obidoxime or pralidoxime chloride (table 3). Slow intravenous administration is recommended to minimize side effects that include: nausea and hypotension (obidoxime) or hypertension, headache, blurred vision, nausea, and vomiting (pralidoxime chloride). Diazepam (or midazolam) should be given repetitively (0.2 and 0.1 mg/kg, respectively, or more) until the complete cessation of convulsions is achieved.

Hemodynamically, children are at a greater risk than adults, since they have less fluid reserves, perspire more, and more quickly dehydrate following vomiting and diarrhea. Their cardiac output is rate dependent. Prompt

fluid resuscitation, epinephrine or dopamine, and careful continuous hemodynamic monitoring is necessary in children who have undergone a combined intoxication-trauma event.

Pain control and satisfactory sedation in the pediatric population is as essential as in adults, perhaps even more so due to emotional repercussion of the child's restlessness on the parents. Most techniques are acceptable in order to reduce pain in children. Due to the abundant secretory and the increased peristaltic effects of the NA or PYR treatment, rectal and nasal routes of drug administration are not likely.

As stressed for adults, general anesthesia is probably the preferred choice in intoxicated and multiple traumatized children due to the anticipated minimal patient cooperation in this scenario. Decisions regarding regional anesthesia in the pediatric population should undergo the same considerations as with adults. Conscious sedation, which is often difficult if not impossible in young children, may be even more problematic in this scenario.

Summary

In preparing this manuscript on providing acute and anesthesia care for patients with conventional injury associated with nerve agent intoxication, we were appalled to discover how little is known. We tried to glean relevant information from publications on related subjects and adapt it to (what are still thankfully) theoretical situations. We did not address the issue of whom to treat when facilities are limited or how to extend the resources to better accommodate suddenly colossal needs. If nothing more, we discovered the enormous complexity of the problem and hope that others will take these first steps much further so that, one day, we will be prepared—hopefully, in vain.

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