

Chapter 30

ANESTHESIA FOR CASUALTIES OF CHEMICAL WARFARE AGENTS

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INTRODUCTION

Chemical agents (ie, substances intended for use in military operations to kill, seriously injure, or otherwise incapacitate through pathophysiological effects^{1,2}) were first used on a wide scale in modern times during World War I. Although in recent years the demise of the Warsaw Pact has markedly lessened the threat of a major war fought with unconventional weapons, the same cannot be said for what may happen in the Third World. In fact, there is evidence that chemical agents have been used in at least seven military actions since 1965 (Exhibit 30-1). While the list of chemical warfare agents most likely to proliferate is not especially long (Exhibit 30-2), there is nothing to say that a country seeking to develop a surreptitious chemical warfare capability may not use a nontraditional agent as a weapon. Even traditional agents may be used in a nontraditional manner. An excellent example of this is Iraq's use of the *mixture* of GB (sarin) and GF (this agent does not have a common name), which together pose a threat via both the respiratory and the transdermal routes of exposure. As treaties banning the use of chemical warfare agents become more numerous, the more likely we are to encounter the unexpected.

The trauma anesthesia provider is usually concerned with the management of casualties injured by physical forces such as blunt and penetrating

injury and blast.³ The American College of Surgeons' standard Advanced Trauma Life Support (ATLS) teaching⁴ is geared to rapid assessment and management of such casualties of conventional warfare. The concept of injury from chemical agents, however, extends the notion of trauma into a new and often more difficult area, where the injury may not always be immediately obvious and may also still be developing during the period of initial assessment. Since the risk of injury from chemical agents in warfare has not diminished in recent years, the military anesthesia provider must always be prepared for the possibility that casualties might suffer from chemical as well as from physical trauma. To a certain extent, the existence of thermal injury in warfare, an injury so very different from the much more common ballistic trauma that has historically dominated warfare, serves to remind us of the need to be prepared to treat unusual injuries. The absence of chemical casualties in World War II and subsequent actions where North Atlantic Treaty

EXHIBIT 30-1

ALLEGED USES OF CHEMICAL WARFARE AGENTS IN THIRD-WORLD COUNTRIES BEFORE THE PERSIAN GULF WAR

Egypt in South Yemen in 1963–1968

Vietnam in Laos, 1975–1978

Ethiopia against Eritrean and Somalia-backed rebels, 1976– ?

Vietnam in Cambodia, 1978– ?

China and Vietnam, 1979

Iraq against Iran, 1984–1988

Iraq against the Kurds, 1988

EXHIBIT 30-2

CHEMICAL AGENTS MOST LIKELY TO BE PROLIFERATED

Nerve Agents

GA: Tabun

GB: Sarin

GF: (no common name)

GB/GF Mixture

Vesicant Agents

HD: Sulfur mustard

Choking Agents

CG: Phosgene

Blood Agents

AC: Hydrogen cyanide

Incapacitating Agents

BZ: (no common name)

Vomiting and Riot Control Agents

DM: Adamsite

CS: Tear gas

Organization forces were involved has perhaps induced a false sense of security. However, there have been other wars in which chemical weapons have been used with devastating effect.⁵⁻⁷ Fears during the Persian Gulf War (1990–1991) highlighted real problems posed by the threat of chemical weapons and enforced new thinking about management of chemical casualties. This was particularly true for anesthesia, and at the time of writing there is again an increased awareness among military medical officers of the potential problems.⁸

The nature of chemical weapons and the formal management of chemical casualties are discussed in *Medical Aspects of Chemical and Biological Warfare*, a volume of the *Textbook of Military Medicine* series, and will not be further discussed here except to mention that the two main chemical threats are

- nerve agents, which kill by causing respiratory paralysis due to their irreversible inhibition of acetylcholinesterase, with consequent accumulation of acetylcholine in nicotinic and muscarinic receptors, and
- vesicants, of which the sulfur mustards are best known, and which incapacitate by causing second-degree chemical burns of the skin.

This chapter covers some of the particular problems posed to military anesthesia providers by the management of the chemical injury itself and by surgical anesthesia for trauma casualties who may also have been exposed to chemical agents. With the ever-increasing number of agents now regarded as potential threats, the approach will be to look at the injury primarily from a pathophysiological standpoint rather than from that of agent specificity.

In general, the involvement of the military anesthesia provider will focus on three broad categories of casualties:

1. those with potentially fatal exposure to a chemical agent, who need immediate, life-saving airway management but who will not require a general anesthetic;
2. those with combined ballistic and chemical agent injuries, who will require anesthesia for the management of the conventional injury; and
3. those who have received pyridostigmine prophylaxis against chemical agents, and who will also require anesthesia for the management of a conventional injury.

Chemical injury may affect almost all the systems of the body but particularly the respiratory and nervous systems. Military anesthesia providers may be directly concerned with these in all stages of management of the wounded, including resuscitation, preoperative stabilization, perioperative and postoperative care, intensive care, and recovery. Chemical injury can affect all these stages, creating clinical problems in their own right and complicating conventional management of injuries that require surgery. Anesthesiologists, as a result of their training, are well placed to grasp the clinical problems arising from chemical injury. The pharmacology and toxicology of the agents will be familiar, as will the nature of the neuromuscular paralysis and respiratory complications such as pulmonary edema and respiratory distress syndrome, which are the life-threatening aspects of chemical injury.

Conventional teaching of chemical warfare injury has often tended to view the subject in isolation. No doubt based on the initial use of poison gas in 1915, the use of chemical arms is often viewed as a special event that will create mass casualties from only one cause. This ignores the subsequent use of poison gas in World War I, wherein the gas was usually disseminated from shells fired in conjunction with conventional high-explosive shells. Thus, casualties with combined ballistic and chemical injuries occurred. Exactly how common such casualties were in World War I is not known. However, of the 546 American soldiers who died following exposure to gas in the period March to November 1918, 6% also had ballistic injuries.⁹ Given the tactical doctrine of chemical agent powers such as the former Soviet Union, which took an integrated approach to the use of chemical weapons (seeing them as part of the ordinary armamentarium available to field commanders, as opposed to being special “weapons of mass destruction”), combined ballistic and chemical casualties should be expected whenever chemical weapons are used.¹⁰ During the Iran–Iraq War, when chemical agents were used the most extensively since World War I (Exhibit 30-3), chemical weapons were also used in a localized, tactical way, particularly as part of defensive infantry actions. The consequence of these developments is that wounding by chemical agents should not be viewed in isolation. It may now be appropriate to think of wounding in three main classes:

1. conventional traumatic wounding, where the tissues are disrupted by externally impressed forces;

EXHIBIT 30-3

IRANIAN EXPERIENCE WITH CHEMICAL WARFARE AGENTS

During the Iran-Iraq War, modern medicine was applied to the treatment of injuries caused by sulfur mustard, tabun, Lewisite, and the biological agent mycotoxin.^{1,2} Although data are limited, there are a number of lessons that we should note. The most unexpected was the surprisingly low mortality: fewer than 1% of the estimated 27,000 Iranian chemical casualties.³

Troops with organophosphate exposure fell into four categories. Those with the greatest exposure died in the field. The number appears to have been very small even though most of the Iraqi attacks were made against unprotected Iranian troops. Those most severely injured who reached medical aid were unconscious and unresponsive, and often in respiratory arrest. The seriously intoxicated had symptoms of dizziness, disorientation, anxiety, salivation, and respiratory difficulty. Those with relatively mild symptoms were often physically difficult to manage because of their disorientation. By far the largest number of casualties required no treatment other than decontamination.

Treatment of mustard exposure during the Iran-Iraq War reflects the experience gained in the management of burn wounds during the 80 years since World War I. Treatment begins with early and thorough decontamination. Early in the course of injury, blistering may not be present. Still, removal of contaminated clothing is important to limit the casualty's contact time with the agent. Shaving of the affected areas followed by washing mechanically removes and dilutes the agent. Aspiration of blisters, removal of necrotic tissue, and treatment of the skin lesions with silver sulfadiazine cream forms the basis for treatment of skin injury. Respiratory exposure to mustard creates its own set of problems. Depending on the degree of injury, the treatment must be adjusted to the degree of injury. Humidified air or oxygen helps to prevent airway obstruction. Bronchodilators, mucolytics, and expectorants are useful. In cases of serious injury, mechanical ventilation with positive end-expiratory pressure and acid-base balance control are used to support the casualty until the injuries resolve. Injury to the eyes is treated with irrigation and sodium sulymid. Pain is treated with systemic medications. Because of weight loss, often in excess of 10 kg, nutritional support is instituted to help reduce the significant mortality associated with negative nitrogen balance. Once the patient reaches a setting for definitive care, therapy is divided into two parts: a general supportive treatment for sepsis and dehydration, and treatment to eliminate toxins from the body.¹

Significant observations from the Iran-Iraq War include the following:

- Decontamination, using soap and water and shaving body hair, was done early. This protected medical personnel and simplified further treatment.
- Comatose casualties of nerve agents who did not have cardiovascular problems were treated with large doses of atropine, 50 to 200 mg administered intravenously. Most casualties received 2 mg every 8 hours. Comatose casualties with significant cardiovascular deterioration (such as bradycardia after 2 mg of intravenous atropine) were most often found not to survive.
- Mustard, although it dates from World War I, continues to be an important chemical agent. It is a vesicant but also has effects on multiple organ systems.

(1) Colardyn F, de Keyser H, Ringoir S, de Bersaques J. Clinical observation and therapy of injuries with vesicants. *Journal de Toxicologie Clinique et Experimentale*. 1986;6(4):237-246. (2) Kadivar H, Adams SC. Treatment of chemical and biological warfare injuries: Insights derived from the 1984 Iraqi attack on Majnoon Island. *Milit Med*. 1991;156:171-177. (3) Hammick M. All stick and no carrot. *International Defense Review*. 1991;(Dec):1323-1327.

2. toxic wounding, where the body systems are poisoned; and
3. environmental wounding, where the body is damaged by excesses of heat and cold.

Casualties may occur from any combination of all three categories.

In a mixed chemical and conventional environ-

ment, the number of casualties with combined (both conventional penetrating and chemical) wounds could be considerable. Not only will these numbers cause potential problems for military anesthesia providers, but other aspects of combat casualty care will also be affected. One study¹¹ used the U.S. Marine Surgical Data Base from the Vietnam War to calculate a figure of potential protective mask failures secondary to conventional wounds of the head

and neck (including the trachea, oral cavity, etc). These researchers predicted that 34% of casualties presenting at a hospital would have wounds that interfered with proper sealing of fielded gas masks.

Since this study makes no attempt to consider wounds that would disrupt other components of mission-oriented protective posture (MOPP) gear, 34% may indeed be a conservative estimate.

ASPECTS OF TOXIC AGENTS OF IMPORTANCE IN MILITARY ANESTHESIA

Recent changes in thinking about the status and definition of toxic warfare agents are of particular importance to military anesthesia providers. Conventionally, riot control agents, herbicides, smoke, and flame are excluded from the definition of chemical agents, although their clinical effects (ie, they kill, seriously injure, or otherwise injure via their pathophysiological effects) bring them within the classical definition of chemical agents. *Biological* agents, on the other hand, are defined as living organisms, the use of which is intended to kill or incapacitate man in warfare.² Under the 1972 Biological Warfare Convention, toxins, which originally could only be produced by living organisms, were included with the biological agents, despite the fact that they are, in fact, chemical substances with unusually high molecular weights.

Although we could argue that all agents designed to incapacitate or kill are, by definition, biological, since the target is man and not his machines, the traditional view of chemical and biological agents has persisted. Clinically, however, the separation of chemical and biological weapons has now become increasingly difficult: new technologies have expanded the number of potential agents in both classes—particularly in the toxins, which lie midway between the two. Developments in biotechnology mean that the synthesis of toxins is now

feasible, and that their use as sophisticated chemical agents is more likely.¹²

The Spectrum of Toxic Hazards in Warfare

Medically, it is now desirable to integrate traditional definitions of chemical and biological agents into a unified concept known as the chemical-biological warfare spectrum of toxic agents. This is shown diagonally in Exhibit 30-4, where the agents are arranged in order of ascending molecular weight, with conventional chemical agents on the left and the self-reproducing agents such as bacteria and viruses on the right. Toxins and other agents of biological origin occupy the middle.

The spectral, rather than the agent-specific, view is important clinically because pathophysiological mechanisms that should be considered in medical management are common to agents from different parts of the spectrum. Neuromuscular paralysis and pulmonary edema are two examples. Failure of the neuromuscular junction, for example, can be caused by two agents as chemically different as a nerve agent and botulinum toxin. The clinical result, however, is the same, and in severe cases the primary lifesaving measure is artificial ventilation. Similarly, there are many agents of which the end result is pulmonary edema. The spectral concept is a reminder to military anesthesia providers that

EXHIBIT 30-4

THE SPECTRUM OF CHEMICAL-BIOLOGICAL WARFARE AGENTS

Low Molecular Weight	—————▶	High Molecular Weight
Nerve agents	Neuropeptides	Bacteria
Pulmonary irritants	Toxins	Viruses
Vesicants		Rickettsiae
Cyanogens		

Adapted with permission from Baker DJ. Chemical and biologic warfare. Part 2. In: Baker DJ. Extreme environmental conditions. In: Grande CM, ed. *Textbook of Trauma Anesthesia and Critical Care*. St. Louis, Mo: Mosby-Year Book; 1993: Chap 108: 1331.

medical management must respond to system dysfunction, not simply to etiology.

Characteristics of Toxic Agents

The characteristics of toxic agents may be divided into the operational and the pathophysiological. The operational aspects are not discussed in this chapter. The pathophysiological aspects of toxic agents are of particular importance to military physicians, however, and include (a) toxicity, (b) latency of onset, and (c) transmissibility.

Toxicity

Toxic agents can kill or incapacitate. The biological effects of potential agents may be estimated from animal studies and data from accidental exposure, but there may be considerable difference from one species to another. The clinical importance of toxicological data is to give some idea of the substances' hazards to man. There are a number of ways of expressing toxicity of agents (Table 30-1); the following are the most common:

- *Ct* is the product of the concentration of an airborne agent multiplied by the time it was inhaled, given a standard rate of respiration. The *Ct* product applies to the middle range of exposure but is inaccurate at very high or very low levels. The units of *Ct* are

mg • min/m³. The relationship of *Ct* to absorbed dose is a function of the rate of respiration or the total exposed skin area. This should always be specified when quoting *Ct* values, and is conventionally accepted as 10 to 15 L/min.

- *LC*₅₀ and *IC*₅₀ are the *Ct* values for a specified route of absorption that will kill (lethal, L) or incapacitate (I) 50% of the exposed population.
- *LD*₅₀ and *ID*₅₀ are the doses for a specified route of absorption that will kill (L) or incapacitate (I) 50% of the exposed population.

Latency

Latency of action is a clinically important property of toxic agents. All agents have a latent period, ranging from a few seconds in the case of cyanide to several hours in the case of some vesicants. Biological agents such as *Brucella* can have a latent period as long as 3 weeks. A patient presenting with few symptoms after exposure may develop more, and more dramatic, symptoms later. Because of this, detecting the use of a toxic agent by the immediate effects on those who have been exposed may not always be possible. Specific latency may be modified by physical factors such as ambient temperature and the amount of exertion after exposure. Latency often decreases as absorbed dose increases.

TABLE 30-1
RELATIVE TOXICITIES OF SOME IMPORTANT BIOLOGICAL AND CHEMICAL WARFARE AGENTS*

Agent	<i>LC</i> ₅₀ (mg • min/m ³)	<i>LD</i> ₅₀
Botulinum toxin [†]		0.15 µg/kg
Soman	40–60	0.025 mg/kg, IV
Sarin	70–100	0.01 mg/kg, IV
Tabun	150	0.08 mg/kg, IV
Cyanide	2,000–5,000	1.0 mg [‡]
Sulfur mustard	1,500	100.0 mg/kg

* Values are based on experimental and extrapolated data from accidental exposure. Toxicities are expressed as *LC*₅₀, the median lethal exposure delivered by inhaling a concentration *C* for a time *t* in minutes; and *LD*₅₀, the conventional median lethal dose.

[†]Estimated respiratory value for man

[‡]Respiratory value

Adapted with permission from Baker DJ. Chemical and biologic warfare. Part 2. In: Baker DJ. Extreme environmental conditions. In: Grande CM, ed. *Textbook of Trauma Anesthesia and Critical Care*. St. Louis, Mo: Mosby-Year Book; 1993: Chap 108: 1332.

Transmissibility

Toxic agents may affect not only the casualty but also the casualty's medical attendants. In the case of biological agents, the risk of transmission by infection is widely recognized. For chemical agents, the risks are of contact and inhalational transmission to medical personnel if the casualty is not

properly decontaminated. Transmissibility is an important characteristic that distinguishes toxic from conventional weapons. *All* casualties of toxic agents must *always* be regarded as risks to their attendants, who may not themselves have been involved in the original attack. This point has considerable significance for the operating theater team involved with the management of such casualties.

PROTECTION, DETECTION, AND DECONTAMINATION

Protection against chemical warfare agents and their detection and decontamination are considered in detail elsewhere,¹ but it is essential that military anesthesia providers be familiar with these concepts, as they affect field anesthetic practice in many ways.

It is the policy of the U.S. military not to perform surgery in a contaminated environment. The casualty should be adequately decontaminated before being taken into the preoperative area or operating room. Clothing should be removed, and the skin and hair decontaminated with hypochlorite. A casualty should not enter the "clean" operating room or the collective protective ensemble (CPE) until decontamination is accomplished; once this is done, the danger from contamination is nil.

Although the desired aim of field anesthesia is to work either on decontaminated casualties or in some form of CPE, it may be necessary in extreme circumstances for hospital-based anesthesia providers to work in an individual protective ensemble (IPE, which is the British equivalent of MOPP gear), particularly in the early stages of resuscitation and triage. Since individual protection involves isolating the operator from the contaminated environment by means of a protective suit and respirator, it follows that many of the normal tactile skills available to the anesthesia provider will be lost or severely impaired, particularly since the casualty may also be similarly isolated. In full MOPP gear, even assessing for something so simple as the casualty's color will be difficult. Simple pulse measurement may not be possible, although radial pulses are palpable through an Mk 4 suit (ie, a kind of IPE) when inner gloves are left out of the operator's ensemble (—*DJB*, personal observation, 1990).

It is clear that only the simplest lifesaving measures are available to the military anesthesia provider in full MOPP gear, although these must include definitive securing of the airway. If necessary, it may be necessary to break the casualty's own IPE to gain access since the danger of airway obstruction outweighs the consequences of further con-

tamination—particularly where there is no direct hazard from a liquid agent. Nevertheless, a surgeon who operates on a contaminated casualty risks spreading contamination into the casualty, a very bad practice indeed.

Although CPE offers greater freedom to work on casualties contaminated with toxic agents, anesthesia providers should be aware of the limitations of collective protection and the importance of careful decontamination, and check the casualty's contamination monitoring before entering the CPE. Experience from the 1991 Persian Gulf War emphasizes the cramped conditions of anesthesia providers working in CPE.⁸ The transit period for any patient through the airlock system is particularly dangerous since it may not be physically possible for a paramedical or anesthetic attendant to be present.

Toxic agents may be delivered as vapor, liquid, or a particulate or liquid aerosol. The possibility that chemical agents can be absorbed onto a carrier dust that will deliver point concentrations of agent directly to the alveoli is an ominous new development. For the anesthesia provider dealing with a potentially contaminated patient, the risks are from direct contact with liquid agent on the patient's clothing, from the vapor the liquid emits, and from reaerosolization of powders.

The simplest method of detecting liquid agents uses special detector papers (although the range of agents detected is limited at this time). The most useful technique for vapor analysis available for use in the operating room is the chemical agent monitor (CAM), which detects nerve and vesicant chemical warfare agents and is used to identify the presence of chemical agent vapors in decontamination operations. This device uses ion-cluster acceleration as the basis for analysis. This technique is similar in principle to mass spectrometry but depends on forming hydrated ion clusters with the toxic agent rather than on accelerating small ions. In CAM, the vapor is sucked into a sampling port, where a radioisotope is used to ionize the toxic agent to form the ion clusters. These are then

accelerated down a high-voltage drift tube and the collected current characteristics are analyzed at one end. In its original form, CAM could be preset to detect either mustard or nerve agent. A modification allows detection of several other agents, all of which can be detected using the drift-tube technique. CAM may be used preoperatively to check the decontamination of patients. One problem that may arise is the slow clearance time of the instrument when background levels of agent are high. Individual chemical agent detectors (ICAD), worn by individual medical personnel, may provide the earliest warning while contaminated patients are being handled. The ICAD will identify nerve, blister, blood, and choking agents and will warn by audio and visual alarms.

The possibility that chemical agents are absorbed onto dusts, or that toxins are delivered as solid aerosols, should be considered with the greatest care. The presence of dust on a patient should be treated with suspicion, particularly since there is no simple toxin-detection device available and these agents are likely to be delivered in solid aerosol form.

If liquid agent is on a casualty, careful decontamination is required. There are two main meth-

ods, wet and dry. Wet decontamination involves the use of oxidizing solutions containing hypochlorite, which effectively oxidizes liquid agents such as mustard and nerve agents. Thickened nerve agents such as thickened GD may have a consistency similar to that of glue and require scraping off before decontamination can proceed further. Dry decontamination (which is not currently used by U.S. forces) uses fuller's earth, an absorbent clay, to remove liquid agent. It should be understood that absorption and removal of the chemical agent does not decrease the agent's toxicity, so care must be taken with the discarded material. Fuller's earth is available in puffer bottles and impregnated pads that may be applied directly to the contamination. The proper sequence of decontamination consists of first removing clothing, then decontaminating the skin. Following decontamination, it is essential that the patient be monitored carefully to allow further medical intervention. An important point is that in serious toxic injury, the normal ATLS processes should be dynamically integrated with the decontamination processes. Proper assessment and definitive airway management will be difficult until decontamination has been achieved.

SITES OF INJURY BY TOXIC AGENTS

In traumatic injury, the mechanism of injury may be known and often will be a useful predictor of the damage.¹³ Similarly, the knowledge that a toxic injury has been caused by a particular agent (eg, an organophosphate) will alert the anesthesia provider to a specific pattern of damage. Knowledge of the nature of the toxic agent is more important than knowledge of the nature of a traumatic force; however, although information may be available at primary casualty assessment, it cannot be guaranteed. Casualties with immediately life-threatening conditions such as apnea or cardiac arrest should receive immediate treatment before decontamination. Decontamination typically takes 10 to 15 minutes, but death from respiratory failure due to exposure to nerve agents can occur within 5 minutes of exposure. In fact, respiratory support must begin before the casualty is brought to the hospital—or to the battalion aid station, for that matter. The casualty will not wait until he arrives at the medical facility to stop breathing. Nevertheless, excluding life-threatening emergencies due to exposure to chemical agents, it is helpful to classify toxic injury in terms of the damage that may be caused by a range of different agents at key anatomical sites rather

than simply as a pattern of injury from a specific agent.

The Skin and Viscera

The skin may be affected by vesicants and toxins. Many agents acting on the skin exhibit considerable latency. Although damage to the skin may be classed as incapacitating rather than life-threatening, the agents concerned, if inhaled, may have additional serious effects on the respiratory tract. Therefore, during assessment, skin lesions should be regarded as a warning of possible accompanying respiratory damage. Sulfur mustard was the vesicant most widely used in World War I. Much clinical experience was gained at the time, but since then, there have been only isolated case reports in which the effectiveness of modern medical therapy can be assessed (see Exhibit 30-1).¹⁴

The viscera may be affected by vesicants if ingested, and by nerve agents following local or systemic poisoning. Ingestion of nerve agents will produce particularly marked intestinal actions, which are probably of central nervous system origin rather than due to local cholinergic action.

The Central and Peripheral Nervous Systems and the Eyes

The central nervous system is affected by a wide range of agents including nerve agents and toxic neuropeptides. Central nervous system symptoms following nerve agent intoxication will be accompanied by peripheral nervous system symptoms in both the voluntary and autonomic systems. Symptoms caused by neurotoxins, however, may be varied, ranging from modification of thought processes and mild delusions to frank coma. A careful assessment of the casualty's level of consciousness is therefore of great importance in the assessment of any toxic casualty. Again, the latency periods will be variable and observation over a lengthy period may be required. At the level of the brainstem, the central nervous system is affected by nerve agents that produce central respiratory failure, and also by cyanogen agents.

Paralysis caused by nerve agents is accompanied by other signs of poisoning (eg, miosis, excessive secretions), and the differential diagnosis from other types of paralysis such as that caused by neurotoxins is not difficult. Paralysis is accompanied by apnea, so an unventilated patient with paralysis is unlikely to be seen at the hospital level. Paralysis from nerve agents lasts 2 to 3 hours at most and should not be confused with the more prolonged paralysis caused by other agents such as botulinum toxin.

The peripheral motor and autonomic nerves are the sites of action of nerve agents and neurotoxins. Neuromuscular paralysis will therefore require differential diagnosis among several possible causes both prejunctional and postjunctional. This may be facilitated by the use of nerve stimulation techniques, which are discussed later in this chapter.

Vesicant agents cause damage to the eye and loss of vision by blepharospasm and corneal ulceration. Nerve agents may produce a variable loss of visual acuity due to miosis and central nervous system

effects on the visual pathway. Loss of accommodation follows spasm of the ciliary muscle.

The Respiratory Tract

Toxic agents may seriously affect all stages of respiration (Table 30-2). In toxic injury, the respiratory tract is particularly vulnerable and its management must take a high priority. Careful clinical examination is of vital importance. While examinations such as radiography and blood gas analyses may be available, simple clinical examination will reveal much of value and must be undertaken as soon as the patient is decontaminated and out of MOPP gear. Five important points to remember are the following:

1. The presence of burns on the skin may indicate similar lesions within the respiratory tract.
2. The casualty's color and the nature of the respirations may point to impending respiratory failure.
3. The presence of paradoxical respiratory movements may indicate upper respiratory blockage of large and small airways.
4. The presence of rales at the bases of the lungs will indicate the development of pulmonary edema.
5. The presence of pathological amounts of secretions in the airway in a casualty who is likely to have been exposed to a nerve agent is strong evidence that too little atropine has been given.

Certain toxins as well as inhaled vesicants have particularly short latency periods, but the latency of onset of symptoms in the chest after toxic injury may be very variable. Any casualty with a suspected respiratory injury should be admitted to a hospital for a mandatory 24-hour observation, during which the respiratory tract should regularly be assessed for the development of signs.

MANAGEMENT OF ANESTHESIA AFTER TOXIC INJURY

The management of toxic casualties is an unfamiliar task for most anesthesiologists, but the specialty should be involved at the earliest stages of planning of facilities to deal with the problem. Besides formulating plans to deal with mass or limited casualties, planning must include flexibility for the effects of unexpected chemical casualties on the

operation of a forward surgical facility. Although intelligence may give good warning of a toxic attack, the information cannot be guaranteed, particularly in rapid-response operations. All ordinary anesthetic and surgical procedures are hampered by the chemical environment, either from the results of an attack or simply from the threat of

TABLE 30-2
EFFECTS OF TOXIC AGENTS ON RESPIRATION

Respiratory Component	Effect	Toxic Agent
Central Nervous System	Depression of respiratory drive and convulsions leading to apnea	Nerve agents, cyanide, neuropeptides
Peripheral Nervous System	Neuromuscular paralysis of respiratory muscles	Nerve agents, neurotoxins
Nasopharynx	May become blocked by excess secretions Prodromal rhinitis and rhinorrhea Sneezing	Lung-damaging agents, nerve agents Vesicants Early symptom of mustard
Larynx	Irritation, laryngeal spasm	Upper-respiratory irritant lung-damaging agents Riot-control agents, particularly CS and CR (tear gas) Nerve agents (theoretical)
Large Airways	Blocked by secretions Blocked by inhaled vomitus Sloughing of walls of trachea and main bronchi, produces "pseudodiphtheritic" membrane, serious cause of large airway obstruction, leading to bronchopneumonia and death	Variety of agents Nerve agents Mustard agents
Small Airways	Blocked by secretions Cholinergic innervation affected; bronchospasm (relieved by atropine) Chemical bronchiolitis, followed by serious bronchospasm	Nerve agents Mustard agents
Alveoli	Toxic pulmonary edema	Variety of agents, especially lung-damaging agents (latency 6–24 h) Vesicant agents, particularly if inhaled at high ambient temperatures ¹

¹Willems JL. Clinical management of mustard gas casualties. *Annales Medicinæ Militaris Belgicae*. 1989;3(suppl)1–61:47, 51.

it, enforcing the use of IPE-MOPP. The planning stage should therefore ensure that the possibility of toxic attack is understood, that equipment is designed to be simple and straightforward in use, and that medical and paramedical personnel are adequately trained.

When reviewed, experience in the Persian Gulf War showed that a number of personnel discontinued the use of pyridostigmine without medical advice.¹⁵ Had there been actual exposure to nerve

agents, these troops and their missions would have been at risk. Anesthesiologists, particularly those in forward areas, are among the most suitable medical personnel to educate the troops to the necessity of using such pretreatment as pyridostigmine and to allay fears with regard to potential side effects.

U.S. military doctrine does not have anesthesiologists or surgeons checking decontamination procedures. By doctrine, noncommissioned officers do decontamination and watch casualties during that

procedure. The following are potential areas of responsibility in the management of casualties from toxic attack:

- managing casualty reception, including checking of decontamination procedures, particularly for casualties in severe respiratory and neuromuscular distress;
- preoperatively assessing the whole patient, who may be suffering from both traumatic and toxic injury;
- assessing the likely impact of prophylactic measures (eg, pyridostigmine bromide), toxic agents, and therapeutic measures on the subsequent action of anesthetic drugs and agents;
- providing advice to surgeons on the morbidity factors associated with the toxic injury in otherwise uncomplicated surgery;
- managing casualties perioperatively;
- managing postoperative complications, which may be toxic, anesthetic, or surgical, or any combination; and
- managing patients who require postoperative intensive care.

The importance of decontamination has been emphasized previously. However, although decontamination is vital for the safety of casualties and medical personnel alike, it must not be allowed to interrupt the continuous process of resuscitation and assessment during triage. Decontamination and monitoring must at all times be dynamic and integrated with primary and continuing medical care. Initially, the casualty arriving at a surgical facility may have to be managed by medical attendants wearing MOPP gear, but the aim should be to get the casualty into CPE as soon as possible to facilitate examination and initial treatment.

Types of Casualties

The following types of casualties may be anticipated following actions where chemical weapons have been employed:

- traumatic casualties, uncontaminated with chemical agents;
- traumatic casualties, contaminated;
- toxic casualties;
- iatrogenic toxic casualties, produced as a result of the side effects of antidotes to toxic agents;

- combined traumatic and toxic casualties;
- thermal stress casualties (these will usually be suffering from heat stress as a result of wearing MOPP gear, but hypothermia may also occur); and
- psychological casualties (combat stress reaction may be common in toxic warfare).

Triage of Casualties

Triage of casualties with conventional traumatic wounds is considered in detail in Chapter 1, Combat Trauma Overview. It is important, however, to apply a system of triage to casualties affected solely by chemical agents. The following is the authors' suggestion (with the U.S. Army's triage designations in parentheses):

- T1 (Priority I and Priority IA): the casualty requires immediate lifesaving treatment. This will almost certainly involve securing the airway, starting intermittent positive-pressure ventilation (IPPV), and continuing pharmacological measures such as atropine, oximes, and benzodiazepines for nerve agent poisoning. Agents causing this type of immediately life-threatening injury will be nerve agents, lung-damaging agents (ie, phosgene), cyanides, and toxins.
- T2 (Priority II): some delay in management is possible. Respiration may be compromised by direct airway problems and by developing neuromuscular paralysis but not to the extent that immediate intervention is indicated. Placing the casualty in this triage category may be influenced by military intelligence about the toxic agent used. If considerable latency of action is likely (eg, with vesicants and some lung-damaging agents), close observation of the casualty is indicated to look for signs of developing vesication in the airway, and pulmonary edema.
- T3 (Priority III): minimal effects from the toxic agent. The casualty may be returned to duty after a period of observation.
- T4 (Priority IV): expectant treatment category. Casualties will usually be placed in this category because facilities available for their medical care are limited (eg, long-term IPPV) in relation to the facilities needed for a larger number of less-seriously injured casualties. Unlike traumatic wounds, there are few toxic injuries in which

the acute phase cannot be managed in the field given sufficient intensive care resources. However, some chemical injuries (eg, extensive vesicant burns) will require long-term hospitalization, which will not be practical in a field hospital.

Casualty-Management Phases

The anesthesiologist who assesses casualties with toxic injuries for surgery must be aware of the preceding medical management, which should have been documented on the casualty card accompanying the patient. The nature of the agent used, the likely exposure time, pretreatment, and early therapy are of importance. The following five phases may be identified:

1. **Preattack.** Casualties may have been taking pyridostigmine bromide, the drug currently contained in the nerve agent pretreatment sets (which are discussed later in this chapter) if a nerve agent attack was thought to be imminent. The state of MOPP at the time of attack is important.
2. **Self-aid.** Casualties may have administered autoinjectable atropine, oximes, and benzodiazepine before or after a nerve agent attack. The possibility exists that the injection may have been given without subsequent chemical agent attack. Atropine intoxication is a theoretical possibility at this stage, causing the casualty to be confused and compounding his heat stress, although the amount of atropine in three MARK I autoinjectors is unlikely to cause significant confusion in the average 70-kg soldier.
3. **Buddy-aid.** The chemically injured casualty may receive further autoject medication from a comrade, but U.S. military doctrine has no provision or method for a buddy to provide airway management or IPPV in a masked casualty.
4. **Initial medical care (battalion aid station),** including initial triage decontamination and ventilatory assistance.
5. **Hospital level,** including decontamination and monitoring with continued integrated medical support. A full ATLS primary survey should be possible at this stage to establish airway, breathing, and circulation, and to determine disability and exposure. The full ATLS primary survey can

be carried out only in a decontaminated casualty.

During the first four phases, the casualty may be relatively isolated from the medical attendants both by IPE and by the use of casualty bags during transport. Even simple maneuvers such as measuring pulse and respiration may be difficult. At the third echelon, noninvasive monitoring should be possible and may include pulse oximetry and capnography. Simple observations of color and mode of respiration, together with auscultation of the lungs, will provide much valuable information at this time. The anesthesia provider may be actively involved with T1 (Priority I and Priority IA) casualties at the third echelon in securing the airway and assessing neuromuscular deficit. The use of an endotracheal tube with early IPPV and positive end-expiratory pressure (PEEP) may be highly desirable, and a laryngeal mask or esophageal occlusion device may be helpful.¹⁶ (Techniques for securing the airway are discussed in Chapter 3, Airway Management.) It is important with toxic casualties to remember the omnipresent risk of vomiting and aspiration. Pharyngeal and bronchial secretions are a major feature of intoxication by several agents, particularly nerve agents, and although efficient suction for clearance is vital, the presence of excessive secretions indicates the need for more atropine. In fact, one of the end points for atropine administration is minimal secretions.

Preoperative Assessment and Examination

The military anesthesia provider preoperatively assessing any casualty must bear in mind the overall classification of casualties stated above. In particular, the possibility of contamination of a patient who has not yet sustained toxic injury must be considered. In a casualty with combined injuries, the anesthesia provider must remember that the casualty may have received pyridostigmine pretreatment, antimuscarinics such as atropine and oximes after agent exposure, and opiates after wounding. All of these will interact with the conduct of general anesthesia.

Toxic agents may radically alter the normal pattern of anesthesia. It is therefore vital that any preoperative assessment should attempt to gain as much information as possible about the circumstances and timing of toxic wounding, together with any information that might be available about the nature of the agents used. Examination should concentrate on the key respiratory and nervous

system sites that will interfere with subsequent general anesthesia. The possibility of latency of onset of signs and symptoms is particularly important, as these may lead to onset of pulmonary edema or other respiratory pathology during the anesthetic course.

The usual preoperative investigations will be required, but these may usefully be supplemented by some assessment of the level of acetylcholinesterase, which is depressed by nerve and mustard agents. In the field hospital, direct estimation of acetylcholinesterase will be difficult, but whether abnormal serum butyrylcholine esterase (also called plasma cholinesterase) is present can be determined using the dibucaine test, which is familiar to anesthesiologists investigating prolonged, pathological action of succinylcholine in a patient.¹⁷ Butyrylcholine esterase will be depressed by nerve agents to an extent similar to acetylcholinesterase when exposure has been severe and the levels of both enzymes are close to zero. Wherever possible, X-ray examinations of the chest should be performed—particularly after exposure to lung-damaging agents, which carry a high risk of causing pulmonary edema. Radiographic evidence of alveolar membrane damage may lag behind the development of pulmonary edema but may be apparent on auscultation of the chest.

Only limited time may be available for preoperative examination, but care should be taken to determine the casualty's color and the rate and depth of respiration. Diminished air entry to the lungs may indicate the presence of secretions, which are a major problem with nerve agents and indicate the need for further administration of atropine. Bronchospasm and bronchiolitis may be signs of inhaled vesicant agent vapor as well as conventional lung-damaging agents, particularly at high ambient temperatures. Unfortunately, the findings of bronchospasm and bronchiolitis within 3 to 4 hours of mustard exposure indicate severe lung damage, and the casualty should be classified in the expectant category.

Cardiovascular assessment should follow the ATLS procedure, but it is important to note that the normal relationship between pulse and blood pressure in a casualty with traumatic injuries combined with nerve agent poisoning may be totally unreliable, due primarily to administered atropine. In casualties with nerve agent injuries who have been inadequately treated, the normal relationship between pulse and blood pressure may also be absent owing to the widespread action of the organophosphate at vagal and sympathetic ganglionic sites

alike. The alimentary system is unstable following nerve agent poisoning, and the risk of vomiting is high. Simple examination of the extremities will reveal possible fasciculations and weakness following nerve agent exposure. If train-of-four testing is possible at this stage, a characteristic depolarization block with no fade is most likely to be found.¹⁸

Anesthetic Induction, Maintenance, and Recovery

Toxic injury may have serious effects on induction of emergency general anesthesia. Shock and toxic airway injury can both produce ventilation-perfusion inequality, giving rise to less-effective preoxygenation. Therefore, as far as possible, the toxic injury should be stabilized before the start of surgical anesthesia. The responses to the inducing agent will require careful titration; normal doses of intravenous induction agents may not apply. With many toxic injuries, both the risk of vomiting and the need for controlled induction with cricoid compression are increased. If assistance is not available, induction should be performed in the lateral position. The action of succinylcholine will be considerably prolonged if used after nerve agent exposure. This effect will also be noted after pyridostigmine pretreatment, owing to the anti-butyrylcholine esterase action of the carbamate anticholinesterase.¹⁹

The respiratory uptake of anesthetic vapors and alveolar ventilation will be affected by degrees of shunt and pulmonary edema during balanced anesthesia. Careful titration of the balance is required.

The characteristics of nondepolarizing muscle relaxants may be particularly affected in patients poisoned with nerve agents. Since organophosphates cause an increase of acetylcholine at the cholinergic junctions, including the neuromuscular junction, the normal pharmacological actions of nondepolarizing blocking agents will be antagonized. For a severely poisoned casualty, the degree of acetylcholinesterase inhibition will be greater than 70%.²⁰ There is little or no clinical experience regarding the actions of muscle relaxants under these conditions, but the buildup of acetylcholine at the postjunctional folds will antagonize the action of nondepolarizing blocking agents, leading to higher-than-expected doses. A casualty who has suffered severe nerve agent poisoning requiring IPPV may have a sufficient depolarization block from the acetylcholine increase to permit surgery, in which case the use of nondepolarizing blocking agents may be unnecessary. Clinical experience in this area is very scarce. There is, however, a theo-

retical advantage in using nondepolarizing agents in this situation, since the occupancy of the receptor sites by the drug may protect the endplate from long-term postoperative damage.

In field surgery, where the operating load may be heavy, predictability of recovery is very important and is the principal advantage of using balanced anesthesia in this situation. The many possible interactions of toxic agents with the techniques of balanced anesthesia, in which multiple drugs are administered, are likely to disturb this predictability and lead to postoperative complications. The normal physiological indicators of balanced anesthesia, such as pulse rate and blood pressure, may

be compromised by the effects of toxic agents. The reversal of nondepolarizing blocking agents may be particularly affected, and recurrent paralysis may occur following nerve agent poisoning. Generally, the likelihood of continuing postoperative intensive care will be greater when conventional and toxic injuries are combined. Given the potential problems for balanced general anesthesia arising from the effects of toxic agents, there may be considerable advantages in using regional blocks for general surgery in this situation. Spinal and epidural anesthesia may be highly unpredictable from a cardiovascular point of view, where the autonomic nervous system is affected by nerve agents.

TOXIC AGENT COMPLICATIONS OF MILITARY ANESTHESIA

The postoperative complications may be significant in patients whose field surgery is complicated by chemical injury. The most important complications from toxic injury of concern to the anesthesia provider are to the respiratory and nervous systems.

Respiratory Complications

Respiratory complications take the form of damage to the airways and alveoli. Vesicant agent exposure causes slow-healing ulceration of the upper respiratory tract and large airways. If sloughing of the pseudodiphtheritic membrane occurs, there will be blockage of bronchi with subsequent collapse.²¹ Bronchopneumonia is a common sequel to these events and was a primary cause of death from mustard poisoning during World War I. Bronchoscopic intervention may be required in such cases. Cases of mustard inhalation reported from the Iran–Iraq War have shown that mustard will affect the terminal airways, in some cases causing a chemical bronchiolitis. This can give rise to severe bronchospasm, which may present difficulties in weaning from a ventilator (—*DJB*, personal observation, 1988). In some casualties, intractable bronchostenosis developed after several years.²²

Pulmonary edema occurs with vesicants only after extremely high exposure or as a terminal event days after exposure. After an extremely high exposure, patchy pulmonary edema may occur within hours of exposure and is also a preterminal event. It is unlikely that a surgical procedure would be undertaken under either of these circumstances. The value of early IPPV with PEEP and high-dose steroid therapy is controversial. Development of the

adult respiratory distress syndrome is possible, and early recognition of the syndrome is important. The problem of doing so is compounded by the fact that such cases will often be managed in clinically unsophisticated facilities, where blood gas analysis and other routine intensive care investigations may not always be available.

For postoperative casualties with toxic injuries, some form of simple intensive care facility is necessary for the respiratory care of the more severely affected. The equipment required may be simple but should be capable of ventilating casualties who have significant adverse changes in pulmonary compliance. Evacuation of ventilator-dependent patients may be desirable in certain circumstances.

Neurological Complications

The therapy of nerve agent poisoning emphasizes the early use of antimuscarinic drugs and oximes to regenerate acetylcholinesterase, in conjunction with pyridostigmine pretreatment.^{1,23} This regime should be effective in most cases, but severely poisoned casualties will require ventilatory support. If nerve agent intoxication was sufficient to remove all remaining acetylcholinesterase after pyridostigmine pretreatment (about 60% of the original store), a period of time will be required for the carbamylated enzyme to be released at the neuromuscular junction. Total ventilatory support may be required during this period. If pretreatment has been effective, this should last only a matter of hours. The nature of the neuromuscular block during this period will be a classical depolarization with a nondecremental response to train-of-four stimuli at 2 Hz. However, military anesthesia pro-

viders must recognize that long-term ventilatory support, indicative of long-term paralysis, is uncommon. With no pretreatment, individual case reports indicate that paralysis and the need for ventilatory support do not persist for more than 2 to 3 hours.²⁴

The experience with nerve agents is in contrast to what is seen with organophosphate *pesticide* poisoning,²⁵ in which the initial block, during the cholinergic phase, may disappear within a few hours. After about 18 hours, however, the block recurs, this time having the characteristics of nondepolarizing block with a decremental response to train-of-four stimulation monitoring. This recurrent paralysis has been termed the *intermediate* syndrome, and is the phase of neurotoxicity when nerve conduction itself is affected, giving rise to sensory and motor dysfunction. The final phase may be mediated by direct neurotoxic actions of organophosphate pesticides rather than through acetylcholinesterase. The neuromuscular block of the intermediate syndrome may be persistent, lasting in some instances as long as several weeks. It may be analogous to the much-debated concept of dual block seen after multiple doses of succinylcholine.²⁶ If the intermediate syndrome occurs, improvement may be seen in neuromuscular transmission following administration of neostigmine.²⁵ There is supporting evidence, from studies using single-fiber electromyography following low-dose sarin exposure in volunteers, that subclinical, nondepolarizing neuromuscular failure occurs even at modest levels of acetylcholinesterase inhibition 3 days after exposure.²⁷ It is important for military anesthesia providers to know that the intermediate syndrome has *not* been seen in thousands of experimental animals and in the limited number of humans inadvertently exposed to *nerve* agents. Furthermore, recently published experiences with organophosphate pes-

ticide poisoning suggest that the delayed respiratory insufficiency is due to pulmonary complications such as secondary pneumonia rather than to respiratory muscle insufficiency per se.²⁸

The use of diazepam may prevent neurological complications from seizure activity as well as decrease spasm from excessive acetylcholinesterase stimulation.

Nondepolarizing Neuromuscular Blocking Agents in Organophosphate Poisoning

Although the intermediate syndrome has not been described in experimental animals or in humans after nerve agent exposure, it should be kept in mind that the experience with humans is quite limited. It is possible that the intermediate syndrome may become apparent given large numbers of nerve gas casualties. If so, theoretical and experimental considerations suggest the following therapeutic approach. Nerve agents cause a prolonged depolarization at the neuromuscular junction, which may lead to secondary changes in the acetylcholine receptors. One therapeutic possibility to avoid the intermediate syndrome is to block the receptor sites with long-acting, nondepolarizing blocking agents such as curare or pancuronium. Competitive denial of access of acetylcholine to the receptors may alter the processes leading to the development of the intermediate syndrome. With the present state of knowledge regarding the long-term block following exposure to nerve agents, this approach can only be regarded as conjecture. However, the anesthesia provider will feel confident in the use of the nondepolarizing drugs in long-term ventilation in the intensive care unit and will have available a therapeutic tool in an area that has little else to offer at present. Further research on the long-term block is needed before any definitive advice can be given.

PYRIDOSTIGMINE PRETREATMENT AND GENERAL ANESTHESIA

Pretreatment with carbamate anticholinesterases is now an established technique whenever there is a risk of exposure to nerve agents. The drug used at the present time is pyridostigmine bromide, 30 mg given every 8 hours. The first large-scale use of pyridostigmine under field conditions occurred during the Persian Gulf War,¹⁵ based on efficiency studies in animals.²⁹ The complete rationale and use of pyridostigmine pretreatment is described in U.S. Army Field Manual 8-285, *Treatment of Chemical Agent Casualties and Conventional Military Chemical*

Injuries.¹ This use of pyridostigmine may have important consequences of which military anesthesia providers must be aware.

Pharmacology

Pyridostigmine bromide is a dimethyl carbamate compound containing a quaternary amine site. It does not, therefore, readily penetrate the blood-brain barrier. In usual doses, its actions are peripheral, and only high doses might cross the barrier

and have central nervous system actions. Like other carbamates such as neostigmine and physostigmine, pyridostigmine is an anticholinesterase compound. Therefore, it has the same action as the organophosphates, but unlike the latter it forms a reversible complex with acetylcholinesterase. Pyridostigmine has no significant plasma-protein binding, indicating that there should be no drug interactions involving competition for binding sites. Seventy percent to 90% of the absorbed dose is excreted unchanged in the urine. At the normal pretreatment dose of 30 mg every 8 hours, the anticholinesterase level returns to within 10% of normal 12 hours after the last dose.³⁰

Mild and reversible symptoms associated with taking the prescribed prophylactic dose have been well described (Table 30-3).¹⁵ Another study⁸ found that more than 10% of 200 uninjured personnel who were taking pyridostigmine pretreatment reported significant side effects including abdominal cramps, increased volume and frequency of stools, flatulence, increased salivation, sweating, headache, and various eye signs including difficulty in focusing and dimness of vision. Isolated reports of more-serious problems such as hypertension were also reported.⁸ In addition, two women with body weights of 45 to 50 kg experienced increased salivation, severe abdominal cramps, nausea, diaphoresis, and muscular twitching—all signs of pyridostig-

mine overdose. Symptoms were found to usually begin within hours of taking the first tablet and were often decreased if the pyridostigmine was taken with a meal.

Protective Action Against Organophosphates

At the pretreatment dosage schedule, pyridostigmine combines with part of the acetylcholinesterase enzyme store to produce a carbamylated complex, which is resistant to subsequent attack by an organophosphate. If a person taking this regime is exposed to nerve agent in a potentially lethal dose, the remaining free acetylcholinesterase will bind irreversibly to the organophosphate, causing a buildup of acetylcholine. However, the carbamylated portion of the enzyme spontaneously breaks down, regenerating free enzyme and effectively providing an autotransfusion of enzyme at the postjunctional membrane. This process does not require the presence of oxime; oxime has no effect on the carbamate–enzyme bond. This new free enzyme is not attacked by nerve agent, because the latter is rapidly broken down in plasma after exposure. There is a considerable safety margin in normal acetylcholinesterase levels present at the neuromuscular junction, and the amount of enzyme released from the pyridostigmine complex is sufficient to restore neuromuscular transmission. The restoration of enzyme in conjunction with the usual resuscitative measures offers a therapeutic solution to the potentially lethal poisoning by nerve agent.

Interactions Between Pyridostigmine and Drugs Used in General Anesthesia

U.S. Army Lieutenant Colonel Jill R. Keeler has reviewed the possible interactions of pyridostigmine pretreatment on the subsequent management of general anesthesia, based on the known pharmacological activity at cholinergic synapses, and her papers should be consulted for a thorough review of the subject.^{19,31} There is very little clinical information on which to draw to confirm these possibilities. The degree of interaction will be related to the amount of acetylcholinesterase inhibition. At the usual pyridostigmine pretreatment dosage, this is usually 40%. Military anesthesia providers should allow for changes in the normal pharmacokinetic profile produced by delayed gastric emptying caused by factors such as traumatic wounding. In this situation, the degree of enzyme inhibition may be less predictable. The possible effects may best be considered in terms of the anesthetic process.

TABLE 30-3
EFFECTS OF PYRIDOSTIGMINE
PRETREATMENT*

Effect	Range of Incidence (%)
Gastrointestinal symptoms	≥ 50
Urinary urgency and frequency	5–30
Headaches, rhinorrhea, diaphoresis, tingling of extremities	< 5
Need for medical visit	1
Discontinuation on medical advice	< 0.1

*Based on reports from medical personnel providing care to 41,650 soldiers (6.5% women) who took pyridostigmine bromide orally, 30 mg every 8 h for 1–7 d. Drug administration resulted in 483 clinic visits, and use of the drug was discontinued in 28 soldiers.

Reprinted from Keeler JR, Hurst CG, Dunn MA. Pyridostigmine used as a nerve agent pretreatment under wartime conditions. *JAMA*. 1991;266(5):694.

Premedication

In field anesthesia, formal premedication may be comparatively rare. Opioids will often have been administered for pain following wounding. Antimuscarinic drugs are usually given as part of the induction. The cholinergic agonist activity of pyridostigmine would be expected to antagonize the action of such agents as atropine and hyoscine. In most Priority I, IA, and II casualties with either traumatic or toxic wounding or both, the notion of conventional premedication is largely academic; however, the anesthesia provider should be aware of the potential problem and be prepared to administer larger-than-usual doses of atropine.

Induction Agents

Sodium thiopental can provoke asthma in susceptible subjects. Pyridostigmine, through its muscarinic activity, may aggravate this situation but clinical evidence is not available. Thiopental is not considered by some to be an induction agent of choice in a hypotensive battle casualty, particularly when time for preoperative stabilization may be limited. The drug causes a fall in cardiac index, stroke volume, and blood pressure. In theory, pyridostigmine may cause a fall in cardiac output due to its vagal action and subsequent bradycardia. There is, therefore, a risk of synergism between the two drugs, and thiopental may best be avoided. Arylcyclohexamines such as ketamine have an established place in field surgery because they provide good cardiovascular support. Heart rate, contractility, cardiac output, and blood pressure are all maintained owing to sympathetic activity. These will tend to antagonize the muscarinic actions of pyridostigmine. Both pyridostigmine and ketamine increase oral secretions. This may increase the risk of laryngospasm following sensitization of the larynx by ketamine.

Neuromuscular Blocking Agents

Balanced anesthesia involving the use of relaxants with endotracheal intubation and IPPV is highly desirable in field surgery because (a) delayed gastric emptying associated with stress during combat means that patients presenting for operation must be assumed to have full stomachs, and (b) in a situation where casualties may be numerous and the operative flow heavy, predictable anesthesia and recovery are essential. To achieve success when relaxants are in use, the effects of pretreatment on

their characteristics should be considered. As an anticholinesterase, pyridostigmine can affect neuromuscular blockade in three ways: by directly affecting depolarization block, by antagonizing nondepolarizing block, and by effects on repeated stimuli used to assess the degree of nondepolarization block.

Action of Pretreatment on Depolarization Block

Depolarization-blocking drugs such as succinylcholine and decamethonium are structurally related to acetylcholine and work effectively as agonists. In normal neuromuscular transmission, acetylcholine reacts with receptors at the postjunctional folds to produce a depolarization, which induces a muscle action potential in the fiber controlled by the junction. The depolarization is usually short-lived owing to the rapid hydrolysis catalyzed by acetylcholinesterase. Unlike acetylcholine, depolarizing blocking agents are not affected by acetylcholinesterase, and the depolarization they produce lasts for a longer period than acetylcholine lasts. It might be expected that pyridostigmine and the standard depolarization blocking agents would be synergistic in their actions, but the degree of significance of the interaction at the targeted pyridostigmine-induced acetylcholinesterase inhibition level of 30% to 40% has yet to be determined. Apart from considerations of synergism, a more important effect of pyridostigmine is on butyrylcholine esterase. This enzyme is found at many sites in the body, including the plasma, where it is responsible for the normal hydrolysis of succinylcholine. The genetic homozygotic and heterozygotic possibilities controlling the enzyme give rise to the well-recognized syndrome of succinylcholine apnea. Pyridostigmine may cause an unpredictable extension in the duration of action of succinylcholine.

Action of Pyridostigmine on Nondepolarizing Agents

Carbamate anticholinesterases such as neostigmine and pyridostigmine are used routinely to reverse the action of nondepolarizing blocking drugs. They do this by inhibiting the catalytic breakdown of acetylcholine at the postjunctional folds. The concept of giving the reversal drug before the relaxant, however, is far less familiar and may be expected to produce changes in the rate of onset and the minimum level of paralysis produced. Experimental studies³² have indicated that pyridostigmine does not significantly alter the characteristics

of neuromuscular block in adductor pollicis in the isolated human forearm, and therefore the clinical significance may be minimal. Since more central muscles, such as the diaphragm, may have a higher safety margin of neuromuscular transmission, the results on adductor pollicis are a good indicator that pretreatment is unlikely to produce significant clinical effects on the subsequent use of nondepolarizing blocking agents. In practical terms, careful titration of the dose of blocking agents will be necessary to ensure ideal clinical conditions. Electrophysiological studies following pyridostigmine pretreatment have shown little change in jitter, indicating no significant neuromuscular effect of the pretreatment schedule itself.²⁷

Effect of Pretreatment on Neuromuscular Monitoring

Train-of-four stimulation monitoring is widely used to assess the degree of recovery of neuromuscular block. Pyridostigmine has a prejunctional, as well as a postjunctional, action. The prejunctional neuromuscular site is thought to be the determinant of fade through a positive feedback mechanism.³³ Therefore, alterations of the conventional fade-block relationship¹⁸ may be possible, and predictions of neuromuscular block may be inaccurate. Experimental evidence in the isolated forearm indicates that the hysteresis relationship between T1 and T4 (of the train-of-four) during onset and recovery of relaxation (differential fade) is unaltered by pyridostigmine.³¹

Inhalational Anesthetics

The anticholinesterase activity of pyridostigmine may give rise to bronchospasm in patients with

asthmatic tendency. Inhalational anesthetics such as isoflurane, enflurane, and halothane have a bronchodilator effect, which might antagonize any sensitization of the bronchi by pyridostigmine. In addition, the inhalational agents potentiate the actions of nondepolarizing neuromuscular blocking drugs. This may be an advantage in pyridostigmine-pretreated patients in removing the need for increased dosage of relaxant drugs.

Military Clinical Experience

During the 1991 Persian Gulf War, the number of casualties sustained by the alliance forces was relatively low. Some of these were taking pyridostigmine in anticipation of nerve agent attack. In three casualties with gunshot wounds who were taking pyridostigmine pretreatment and who also required surgery, a technique of total intravenous anesthesia using ketamine, midazolam, and vecuronium was used. Atropine premedication was required because of significant salivation. There was no obvious extension of the action of suxamethonium bromide used for intubation, but there were indications that a larger-than-usual dose of vecuronium was required. It is not clear whether this was due to the total intravenous anesthesia technique or to the pyridostigmine pretreatment. The casualties were all operated on at least 7 hours after taking the last dose of pyridostigmine, and by this stage only about 10% of the acetylcholinesterase could be expected to be complexed. Although these findings are anecdotal, they are a useful indicator for general anesthesia following pyridostigmine pretreatment. The observations on the side effects, in particular, are at variance with previous studies, although it should be noted that the battlefield observations were uncontrolled.

SUMMARY

In the past, military anesthetic policy and experience have largely been involved with conventional physical trauma rather than chemical injury. The continuing risk of casualties from chemical warfare agents enforces a wider view, encompassing casualties who may be suffering from physical, toxic, or environmental trauma, or from any combination. Chemical agent injury may affect all body systems, and military anesthesia providers may be involved in its management either directly or as part of the perioperative management of coincident physical trauma. Chemical casualties should be expected at any time during conflict and not just in unique

circumstances, and chemical weapons should now be considered as tactical weapons rather than necessarily as weapons of mass destruction. Preparations for chemical agent casualties should, therefore, be made in all military actions, particularly those involving rapid-response forces in unusual areas.

The concept of chemical weapons has now been extended to cover agents previously described as toxins or biological agents. A spectrum of toxic agents exists, in which agents that differ considerably in their physical nature may have common pathophysiological pathways of clinical damage.

The chemical–biological warfare spectrum reminds military anesthesia providers of the need to respond to the dysfunction of systems rather than solely to the specific management of individual toxic agents. All agents in the spectrum possess three main characteristics: toxicity, latency of action, and transmissibility. The serious consequence of transmissibility is that toxic agents, unlike other weapons, pose a continuing danger to medical attendants down the evacuation line.

Military anesthesia providers must be totally familiar with current teaching about protection, detection, and decontamination of toxic agents. The use of CAM and ICAD will facilitate all practices. IPE-MOPP gear may be required for anesthesia providers working at early stages of casualty management. These protective ensembles will enforce isolation from the casualty and make difficult the contact necessary for simple monitoring and airway management. When the casualty's life is threatened, it may be necessary to remove his respirator to gain access to the airway, since the dangers from the existing respiratory failure may outweigh the risks from further inhalation of the agent. Collective protection offers greater freedom for casualty assessment, resuscitation, and anesthesia, but conditions may be cramped.

Much as the knowledge of the type of trauma sustained may be a useful predictor of the nature of physical injury, so knowledge of the toxic agent may also predict the extent of toxic injury. This is particularly true in the case of long-latency agents, where the symptoms and signs may not yet have fully developed. In some instances, specific knowledge of the agent used may not be available, and treatment should be based on the casualty's presenting signs and symptoms. Toxic agents may affect the skin, viscera, blood, mitochondria, central and peripheral nervous systems, and the respiratory system. In the last category, agents may affect the respiratory center, respiratory muscles, nasopharynx, larynx, large and small airways, and the alveoli. Careful clinical assessment of all systems is vital. Signs present in one system may provide valuable clues about developing pathology in others.

The responsibilities of the anesthesia provider in the management of toxic injury start with planning in the preattack phase. Specific responsibilities include being knowledgeable about the hospital's plans for casualty reception, including decontamination and resuscitation of chemical casualties. Military anesthesia providers will be intimately involved in preoperative assessment of prophylac-

tic measures, toxic agent effects, and therapeutic measures on the subsequent course of anesthesia. They may be asked to advise surgeons on toxic morbidity factors; the perioperative management of casualties with combined conventional and chemical injuries; and the management of toxic, anesthetic, and surgical postoperative complications, including intensive care.

A system of triage must be created for casualties who have been exposed to toxic agents, and conventional triage systems should be modified to take account of toxic factors. Careful preoperative assessment is required, since toxic factors may radically alter the normal patterns of anesthesia. The respiratory and neuromuscular systems are particularly important. Induction and maintenance of, and recovery from, general anesthesia may all be affected by toxic injury and its therapy. A casualty's responses to neuromuscular blocking drugs may particularly be altered after nerve agent exposure. The action of succinylcholine may be prolonged and the nondepolarizers antagonized. Nerve agent paralysis itself may permit surgical intervention but is likely to be unreliable. Given the problems posed to general anesthesia, careful consideration must be given to the use of regional anesthetic techniques; spinal and epidural anesthesia may, however, provoke unstable cardiovascular responses after nerve agent attack.

Postoperative complications may be significant. Serious and frequently fatal damage to the large and small airways can result from the inhalation of droplets or vapor of vesicant agent. Pulmonary edema is a consequence of several toxic agents, including conventional lung-damaging agents (eg, phosgene) and vesicants (eg, mustard gas). Neurological complications may follow nerve agent poisoning. Evidence from organophosphate pesticide poisoning, but not so far with nerve agents, indicates a relapse of neuromuscular paralysis 24 hours after exposure and following apparent recovery with atropine and oxime treatment (the intermediate syndrome). The recurring paralysis is nondepolarizing in nature. There may also be a later stage of peripheral neuropathy. Toxic complications will increase the likelihood of postoperative intensive care.

Pretreatment with pyridostigmine as a prophylaxis against nerve agent poisoning has several implications for military anesthetic practice. Inhibition of butyrylcholine esterase may cause the action of succinylcholine to be prolonged. Although experimental studies have not indicated significant antagonism of the action of nondepolarizing relax-

ants, clinical experience in this area is scarce. Reports of casualties who had taken pyridostigmine, and who subsequently received total intravenous anesthesia for surgery following traumatic, not toxic agent, injuries, indicate that the amount of vecuronium required may possibly be increased. At present, it may be said that pyridostigmine pretreatment adds to the uncertainty of clinical anes-

thesia for incidental operative intervention.

There has been very little recent experience of anesthesia after toxic injury in warfare, and the subject still remains one of speculation. Good planning and familiarity with standard procedures will reduce the undoubted difficulties likely to be encountered in the anesthetic interface with casualties of toxic weapons.

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