The Centers for Disease Control and Prevention urge physicians to become familiar with chemical and biological weapons. Preparedness among neurologists is especially important because several of these agents affect the nervous system. This article reviews 4 agents that have a history of military or terrorist use: cyanide poisons, organophosphate poisons, botulinum toxin, and anthrax. Cyanide and organophosphate poisons are characterized by dose-dependent impairment of neurological function with nonspecific symptoms such as headache or dizziness at one end of the spectrum and convulsions and coma at the other. Neurological examinations help clinicians to differentiate these agents from other intoxications. Botulinum toxin has a delayed onset of action and results in descending paralysis and prominent cranial nerve palsies. Anthrax frequently causes fulminating hemorrhagic meningitis. Early recognition of these chemical and biological weapons is key to instituting specific therapy and preventing casualties within the health care team and the community at large.

Arch Neurol. 2003;60:21-25

Several chemical and biological weapons affect the nervous system, increasing the likelihood of a neurological consultation. Of the many agents that might be employed, this article focuses on cyanide, cholinesterase inhibitors, botulinum toxin, and anthrax because they have prominent neurological manifestations. This article reviews the weapon applications, clinical manifestations, and treatments of these agents.

CYANIDES

Cyanide gases could potentially cause sudden mass casualties. Hydrogen cyanide and cyanogen chloride are highly volatile liquids with boiling points near room temperature. Both are absorbed through the skin and respiratory epithelium. Although hydrogen cyanide has an odor reminiscent of bitter almonds or peach pits, many people are not able to detect this distinctive odor.1 Cyanogen chloride is an irritant with a pungent, biting odor.

The severity of illness and the types of symptoms depend on the level of exposure. A large exposure promptly results in death, whereas a relatively small exposure produces nonspecific symptoms.1 Whether a symptomatic threshold is reached depends on the duration of exposure and the ambient concentration of the compound. These factors largely limit the terrorist use of cyanide gas to a closed environment, such as an office building or subway.

Cyanide poisons act by blocking the electron transport chain, causing an intracellular crisis in adenosine triphosphate synthesis. In cases of substantial exposure, the failure of brain aerobic metabolism results in loss of consciousness within 1 minute (Table). Respiratory depression and cardiac arrest follow within a few minutes. At lesser exposures, neurological symptoms can include headache, vertigo, nausea, seizures, and abnormal breathing. Symptoms can progress to coma over a few hours. Because hydrogen cyanide is excreted by the lungs, a patient’s breath may have the characteristic bitter almond odor. Patients can develop tachycardia and tachypnea, and the pupillary light reflex may be delayed.2 Focal neurological impairments are not prominent.
The diagnosis of cyanide poisoning is difficult, particularly if an individual patient is affected. The differential diagnosis includes carbon monoxide poisoning, exposure to organic solvents, drug intoxication, hypoglycemia, electrolyte disturbances, and a postictal state. Cyanogen chloride induces mucosal irritation and excessive respiratory secretions that are suggestive of organophosphate poisoning. Laboratory studies may show only minor abnormalities. Lactic acidosis with an excessive anion gap should be readily detectable, which Narrows the diagnostic possibilities. A potential clue is higher than anticipated oxygen concentration in venous blood. Serum concentrations of cyanide can be measured, but this test is not readily available in most hospitals. Testing for thiocyanate, the hepatic metabolite of cyanide, might be obtainable at larger medical centers.

The treatment is multifaceted. Decontamination should be performed, given the possibility that residual cyanide may be found on the patient’s skin or clothing. For mildly affected patients who are improving, observation may be sufficient. For patients with more severe poisoning, treatment includes basic life support, supplemental oxygen, and correction of metabolic acidosis. Specific therapies include amyl nitrate, sodium nitrate, and sodium thiosulfate. These drugs are stocked together in cyanide antidote kits (Taylor Pharmaceuticals, Buffalo Grove, Ill). The rationale for this therapy is based on the use of nitrates to induce methemoglobinemia because cyanide ions have a higher affinity for methemoglobin than for the mitochondrial enzyme cytochrome oxidase. Amyl nitrate vapor can be administered either by holding saturated gauze under the patient’s nose and mouth for 30 seconds of every minute or by emptying an ampule in a respirator reservoir. When intravenous access is obtained, amyl nitrate is discontinued, and 300 mg of sodium nitrate is administered at a rate of 2.5 to 5 mg/min. The patient should be monitored for excessive methemoglobinemia, manifesting as cyanosis or shock. Methemoglobin concentration can be measured; a desirable level is between 20% and 30% of total hemoglobin. Although excessive methemoglobinemia can be treated by infusion of 1% methylene blue, this therapy should be avoided because it results in intravascular release of cyanide. When the infusion of sodium nitrate is complete, 12.5 g of sodium thiosulfate is administered. This drug promotes the formation of thiocyanate, which is secreted by the kidneys.

Hydroxocobalamin, a vitamin B12 precursor, is another cyanide antidote. Cyanide has a high affinity for this drug, which leads to unbinding of mitochondrial cytochrome c. Large doses (2.5–5 grams) of hydroxocobalamin are required. As currently formulated in the United States, this translates to large volumes of drug (2.5–5 L), rendering this therapy impractical.

Delayed toxic effects involving the basal ganglia may occur. Parkinsonian features emerge earlier than dystonia. Dysarthria, eye movement abnormalities, and ataxia have also been described. Magnetic resonance imaging may show cavitation of the putamen and globus pallidus. Cortical, cerebellar, and diencephalic changes have also been described. Response to treatment of parkinsonian and dystonic symptoms by dopaminergic drugs is often disappointing because of cell loss in lenticular structures. Intellectual deterioration after cyanide exposure has also been reported.

**ORGANOPHOSPHATES**

Although organophosphates are commonly used as insecticides in agricultural settings, more potent organophosphate compounds, termed “nerve agents,” can be used as chemical weapons. The militarized organophosphates are GA (tabun), GB (sarin), GD (somin), GF, and VX. As vapors, the organophosphates are rapidly ab-
sorbed by the lungs. The interval from exposure until clinical symptoms is brief (Table). Organophosphates act by blocking acetylcholinesterase. The cardiac symptoms of organophosphate poisoning are excessive salivation and lacrimation as well as involuntary urination and defecation ("SLUD"). In addition, patients may complain of dim vision, eye and nose irritation, rhinorrhea, or chest tightness. With large doses, patients can present with seizures or coma. Tachypnea with labored breathing and arterial hypotension can occur. Patients usually have copious oral and nasal secretions. Wheezes and rhonchi may be heard on auscultation of the lungs. Eye findings include miosis and conjunctival hyperemia. Localized muscle fasciculations can be found in areas where organophosphate droplets penetrated skin. Generalized fasciculations can occur with respiratory exposure or with large transdermal exposures. Cardiac conduction abnormalities, in particular heart block, can be detected on electrocardiograms.

Decontamination is particularly important with droplet exposure. Forceful washing and flushing of exposed skin can limit further absorption and also protects health care providers. Clothes should be removed and bagged. Severely affected patients require respiratory support, and atropine reverses bronchial constriction, facilitating mechanical ventilation. Less severely affected patients also benefit from atropine. The usual adult dose, 2 to 4 mg, can be readministered every 5 to 10 minutes until secretions halt. Relatively high cumulative doses of atropine, between 10 and 20 mg during the first 3 hours, are not uncommon, and patients should be monitored for signs of atropine toxicity (delirium, hyperthermia, or increased fasciculations).

Pralidoxime chloride is given in conjunction with atropine. This medication binds acetylcholinesterase, displacing and hydrolyzing the organophosphate. For adults, the dose is 1 to 2 g, administered intravenously in 100 mL of saline, over 15 to 30 minutes. A second dose can be given after an hour if paralysis persists. In critically ill patients, a maintenance pralidoxime infusion (7.5 mg/kg per hour) after a 2-g bolus has been reported safe.10 Very rapid administration of pralidoxime can worsen motor weakness. The organophosphate-acetylcholinesterase complex becomes resistant to oxime therapy in a process termed “aging.” The GD-acetylcholinesterase complex undergoes aging the fastest, with a half-time of 2 minutes.11 The other nerve agents affect a several-hour window during which pralidoxime may be effective. Because the efficacy of oxime therapy diminishes with increasing interval from exposure, pralidoxime should be given immediately. Seizures complicating organophosphate poisoning are usually self-limited. If seizures occur despite administration of pralidoxime, benzodiazepines may be employed.

Neurological sequelae of organophosphate poisoning are numerous. A relapse of weakness can occur 1 to 4 days postexposure. In cases of insecticide exposure, the incidence of this so-called “intermediate syndrome” is approximately 8%.12 Therapy is supportive, and patients may require intubation. Recurrent weakness typically resolves within 5 to 18 days.13 Insecticide organophosphate poisoning can result in a severe polymyopathy that appears approximately 1 to 3 weeks after exposure. This neuropathy is believed to be caused by phosphorylation of the enzyme neuropathy target esterase. Animal studies suggest that exposure to militarized nerve agents would be fatal before sufficient neuropathy target esterase inhibition occurred. In addition to neuropathy, pyramidal signs and symptoms can develop. Long-term impairments of memory, speeded processing, and mood have also been described.

**BOTULINUM TOXIN**

Exemplifying its potency, a lethal dose of botulinum toxin for a 70-kg human is estimated to be approximately 0.09 to 0.15 µg parenterally, 0.7 to 0.9 µg inhalationally, or 70 µg orally. Clinical experience with human botulism derives from cases of accidental botulism poisoning associated with ingestion of spoiled foods, wound botulism, and infantile botulism. Botulinum toxin can be absorbed by either gastrointestinal or respiratory epithelium but does not penetrate intact skin. All 7 types of botulinum toxin (designated A through G) act presynaptically as endopeptidases, cleaving proteins necessary for acetylcholine exocytosis.

Based on inhalation studies conducted in primates and on human food contamination cases, the clinical features of botulism are essentially the same regardless of the mode of absorption. Oral ingestion of purified botulinum toxin is unlikely to produce gastrointestinal distress. Symptoms of botulism appear as soon as 2 hours or as late as 8 days after ingestion (Table). Botulism preferentially affects the cranial nerves, causing ptosis, poorly reactive dilated pupils, disconjugate gaze, facial diplegia, aspiration, and dysarthria. Generalized weakness and respiratory compromise develop. The differential diagnosis of botulism includes myasthenia gravis, tick paralysis, pontine infarction, diphtheria, and the Miller-Fisher variant of Guillain-Barré syndrome. The diagnosis of botulism can be confirmed by sending a serum sample to the Centers for Disease Control and Prevention. Although not immediately helpful, samples should be forwarded to allow typing of the toxin. Characteristic results of electrophysiological studies include normal nerve conduction velocities, normal sensory nerve conduction studies, small motor unit potentials, and an incremental response to repetitive stimulation at 50 Hz. Results of cerebrospinal fluid examination and brain imaging studies are normal.

The only specific treatment for botulism is passive immunization with antitoxin. The immunoglobulins will not reverse existing paralysis, but they may stabilize the deficits. The antitoxin, available emergently from the Centers for Disease Control and Prevention, is active against the 3 most common toxins (types A, B, and E). It is provided in a single 10 mL vial that provides 5500 to 8500 international units of each type-specific antitoxin. The agent must be diluted 1:10 in isotonic sodium chloride solution and administered by a slow intravenous infusion. The antitoxin is of equine origin and urticaria, serum sickness, and anaphylaxis are potential complications. Measures to screen for allergic reactions and desensitization may be necessary. Diphenhydramine hy-
drochloride and epinephrine should be available to treat hypersensitivity reactions. The US Army possesses limited quantities of an investigational heptavalent antitoxin, 18 which might be available in a terrorist attack.

Supportive management of patients with botulism focuses on maintaining ventilation. Guidelines developed for the respiratory support of patients with myasthenia gravis may be followed in the management of botulism. Mechanical ventilation should be strongly considered if vital capacity falls below 15 mL/kg or negative inspiratory force measures less than 20 cm of water. 19 Placement of a nasogastric tube to permit nutrition and hydration is required in patients with bulbar palsy. Patients must be monitored for constipation. For intubated patients, intensive care will likely be protracted. Recovery from botulism occurs by the sprouting of new synaptic terminals. Return of motor function in severely paralyzed patients is protracted and full recovery may require more than a year.

ANTHRAX

Bacillus anthracis is commonly found in agricultural environments. It is a gram-positive aerobic organism that, in the vegetative form, has a poor survival outside of an animal or human host. 20 Sporulated anthrax can survive for decades in a natural setting. All 3 forms of anthrax, inhalational, cutaneous, and gastrointestinal, can be complicated by meningitis. 21,22 The risk of hemorrhagic meningitis in cases of inhalational anthrax is estimated to be as high as 50%. 20 Neurologists may see cases of this presentation.

Most naturally occurring human cases are cutaneous and derive from contact with anthrax-infected animals or contaminated animal products, such as wool or skins. The hands, arms, and face are the most common sites of cutaneous anthrax. A purpuric papule evolves into an ulcer followed by the development of a painless black eschar. The eschar dries and desquamates after 1 to 2 weeks. Patients can have painful lymphadenopathy and sepsis. With treatment, the mortality rate of cutaneous anthrax is low. Gastrointestinal anthrax, also occurring naturally as a result of eating poorly cooked, contaminated meat, manifests with nausea, vomiting, diarrhea, an acute abdomen, or sepsis.

The most serious terrorist threat posed by anthrax is infection by inhalation. For humans, the estimated 50% lethal dose of inhaled spores is 2500 to 55000. 20 Anthrax spores germinate in an environment of amino acids, glucose, and nucleosides. Once germination occurs, symptoms occur rapidly. The replicating bacteria produce toxins, leading to local tissue hemorrhage, edema, and necrosis. The primary site of infection in inhalational anthrax is in the mediastinal lymph nodes. In most cases described, the interval from exposure until the onset of symptoms is less than a week (Table 1). Initial symptoms of inhalational anthrax are fever, chills, myalgia, cough, and sore throat. Substernal chest pain, dyspnea, abdominal pain, nausea, and vomiting are common. Subsequently, patients with inhalational anthrax develop sepsis, hypoxemia, cyanosis, and shock.

Eight of the 10 inhalational anthrax infections from the autumn of 2001 had neurological findings (defined as headache, confusion, blurred vision, visual field distortions, or syncope). Headache (occurring in 5) and confusion (occurring in 4) were the most common manifestations. 23 Elevated cerebrospinal fluid erythrocyte counts may lead the clinician wrongly to conclude that the patient is suffering from herpes encephalitis or a ruptured aneurysm. In addition, reports of anthrax meningitis have shown cerebrospinal fluid leukocyte counts greater than 500/mL and total protein levels greater than 0.4 g/dL. 21,22,24 Gram stains have revealed large gram-positive rods with or without endospores.

Abnormalities on other diagnostic studies include a widened mediastinum on chest radiograph, marked leukocytosis on complete blood count, and the detection of the organism by cultures or gram stains of blood or aspiration of skin lesions. Because anthrax does not lead to an alveolar infection, sputum cultures are likely to be negative for growth of B anthracis. Immunological studies for the antigen or polymerase chain reaction are available at some medical centers.

Cases of anthrax meningitis should be treated with a multidrug regime including ciprofloxacin and at least 1 other agent. Vancomycin hydrochloride, chloramphenicol, and penicillin may be considered. Doxycycline hyclate and clindamycin phosphate should be avoided because of poor cerebrospinal fluid penetration. Anthrax is resistant to ceftriaxone sodium and other third-generation cephalosporins. Treatment may be tailored to individual susceptibilities. Steroids have been suggested as an adjunctive therapy. 25

A vaccine against anthrax is available for military personnel and civilian workers at risk for infection. It requires 6 doses given in series and yearly boosters. The vaccine appears to be effective in protecting against both cutaneous and inhalational anthrax, and it has been given with a low incidence of adverse reactions. 26 However, current supplies of anthrax vaccine are limited.

Because there are no data to suggest person-to-person transmission of anthrax, standard precautions appear adequate. Family members or other persons close to the patient do not need to be treated with prophylactic antibiotics unless there is evidence that they were exposed to spores. Decontamination of the site of the anthrax exposure is a critical public health step. Secondary aerosolization of spores could mean that subsequent exposures could occur if the environment is not decontaminated.

CONCLUSIONS

For many forms of chemical or biological terrorism, neurologists would play an important role in the diagnosis and treatment of the victims. Although we can hope that no attacks will occur in the future, preparedness is crucial to public health efforts. Our attention to these issues can help allay the public’s concerns, fears, and suffering. As neurologists, our participation in this area is a personal contribution we can make to protect human life in these uncertain times.

Accepted for publication March 19, 2002.

Author contributions: Study concept and design (Drs Martin and Adams); drafting of the manuscript (Dr Mar-
tin); critical revision of the manuscript for important intellectual content (Dr Adams).

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