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Neuroterrorism Preparedness for the Neurohospitalist

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Abstract

In this review article, we highlight several potential biologic and chemical agents of "neuroterrorism" of which neurohospitalists should be aware: anthrax, botulism toxin, brucella, plague, smallpox, organophosphates and nerve agents, cyanide, and carfentanil. Such agents may have direct neurologic effects, resulting in encephalopathy, paralysis, and/or respiratory failure. Neurohospitalists should be on the lookout for abnormal neurologic syndrome clustering, especially among patients presenting to the emergency department. If use of such a "neuroterrorism" agent is suspected, the neurohospitalist should immediately consult with emergency department personnel, infection control, infectious disease physicians, and/or Poison Control to make sure the scene is safe and to stabilize and isolate patients if necessary. The neurohospitalist should also immediately contact their local and/or state health department (or alternatively the US Centers for Disease Control and Prevention Emergency Operations Center) to report their suspicions and to obtain guidance and assistance.

Keywords

terrorism, bioterrorism, neuroterrorism, anthrax, botulism, brucellosis, plague, smallpox, nerve agents, organophosphates, cyanide, carfentanil, neurohospitalist, neurologist, preparedness

Introduction

According to the US Centers for Disease Control and Prevention (CDC), "public health infrastructure must be prepared to prevent illness and injury that would result from biological and chemical terrorism, especially a covert terrorist attack."[1] This is especially salient given several biological and chemical attacks over the past few decades, including cyanide in Jonestown, Guyana, in 1978, anthrax through the US Postal Service (USPS) in 2001, sarin gas in Japan in 1995 and Syria in 2017,[2-4] and Novichok in the United Kingdom most recently in 2018.

Following such biological or chemical attacks, health-care providers may be "the first to observe and report unusual illnesses or injuries."[1] Many potential terrorist agents have direct neurologic effects, which may result in encephalopathy, paralysis, and/or respiratory failure. As such, while emergency medical providers are typically thought of as being on the "front-line" during such attacks, consulting neurohospitalists may also play key roles in the recognition of these agents and management of their syndromes.[5]

In this review article, we provide an overview of several biological and chemical terrorism agents that can have significant effects on the nervous system (ie, agents of "neuroterrorism" previously described by Busl and Bleck[5]) in order to better prepare neurohospitalists to clinically recognize and help manage the potential effects of such incidents (Table 1).

Biologic Agents

Anthrax

Cause. *Bacillus anthracis* is a gram-positive, aerobic, spore-forming, bacillus bacteria found in soil that can affect various

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Table 1. Summary of Potential Neuroterrorism Agents and Their Potential Neurologic Manifestations, Diagnostic Methods, and Treatments.

Agent	Potential Neurologic Manifestations	Diagnostic Methods	Treatment
Biologic agents			
Anthrax	Hemorrhagic meningoencephalitis	Clinical presentation and exposure history; bacterial culture; detection of nucleic acid, toxins, or antibodies	TX: Fluoroquinolones and other antibiotics, antitoxin PPX: Fluoroquinolones and other antibiotics, vaccination
Botulism	Descending flaccid paralysis, autonomic dysfunction	Clinical presentation and exposure history; mouse bioassay; detection of neurotoxin	Botulinum antitoxin or immunoglobulin, respiratory support
Brucellosis	Acute: Meningitis, meningoencephalitis Chronic: Peripheral neuropathy, radiculopathy, or cranial nerve palsies.	Clinical presentation and exposure history; bacterial culture; detection of antibodies	Doxycycline and other antibiotics
Plague	Meningoencephalitis	Clinical presentation and exposure history; gram stain; bacterial culture; detection of nucleic acid or antibodies	TX: Fluoroquinolones and other antibiotics PPX: Fluoroquinolones and other antibiotics
Smallpox	Meningoencephalitis	Clinical presentation and exposure history; viral isolation; detection of nucleic acid	TX: Vaccinia immune globulin intravenous (VIGIV), tecovirimat/ST-246, or cidofovir PPX: Vaccination
Chemical agents			
Organophosphates and nerve agents	Acute: Muscarinic and nicotinic neurologic effects (Table 2), seizures Chronic: Intermediate syndrome	Clinical presentation and exposure history	Atropine, 2-PAM, benzodiazepines for seizures, respiratory support
Cyanide	Acute: CNS depression, seizures, coma Chronic: Parkinsonism	Clinical presentation and exposure history; elevated anion gap and lactate level	Hydroxocobalamin (vitamin B_{12a}), amyl and sodium nitrite, sodium thiosulfate
Carfentanil	CNS and respiratory repression	Clinical presentation and exposure history; specific drug assays	Naloxone, respiratory support

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; PPX, prophylaxis; TX, treatment; 2-PAM, 2-pyridine aldoxime methyl chloride.

domestic and wild animals.[6-8] Humans become infected when spores are inhaled (inhalation anthrax), ingested (gastrointestinal anthrax), or inoculated through skin wounds and mucous membranes (cutaneous anthrax). Once in a favorable environment, these spores germinate into active bacteria, which then multiply and produce toxins. Inhalation of aerosolized spores, as in the unsolved 2001 USPS attacks, has the most potential for mass-casualty or terrorist incidents due to its ease of deployment.[3,7,9] However, any route of transmission may eventually lead to hematogenous spread, resulting in septic shock and/or seeding of the central nervous system (CNS), resulting in a hemorrhagic meningoencephalitis.[6-8,10,11]

Clinical presentation. Initial clinical presentation depends on the route of exposure.[6-8] Cutaneous anthrax, which is the most common form and least likely to be fatal, causes a painless red vesicle with surrounding edema which eventually ulcerates and becomes a black eschar. Inhalational anthrax typically begins within 1 week after exposure with nonspecific flu-like symptoms including fever, chills, nonproductive cough, myalgia, and/or fatigue that may progress to pneumonia, pleural effusions, a hemorrhagic mediastinal lymphadenitis, and/or respiratory failure. Gastrointestinal anthrax also presents with fevers and chills, in addition to nausea, vomiting, abdominal pain, and/or bloody diarrhea. It may also involve oral ulcers, pseudomembranes, and severe neck swelling. Any of these 3 anthrax syndromes may progress to septic shock and/or hemorrhagic meningoencephalitis, though the latter is more common with inhalational anthrax. Patients with anthrax hemorrhagic meningoencephalitis (presenting with altered mental status, nuchal rigidity, and/or diffuse subarachnoid and intraparenchymal hemorrhage) can have a mortality rate of over 90%.[6-8,10,11]

Diagnosis. Diagnosis of inhalational or ingested anthrax infection begins with a high index of suspicion, as the signs and symptoms are often highly nonspecific.[6,7] Cutaneous anthrax typically presents with the characteristic skin lesion. Inhalational anthrax should be suspected when a person with occupational exposure or a history of exposure to a white powder develops a respiratory syndrome of unknown etiology, particularly when multiple cases of respiratory distress are clustered in space and time (especially during noninfluenza seasons). A chest x-ray may demonstrate a wide mediastinum, pleural effusion, or simply pneumonia. Gastrointestinal anthrax should be suspected with

the aforementioned symptoms with the presence of a pseudomembranous oral ulcer. Culturing the bacteria from preantibiotic fluid samples is the gold standard for diagnosis, though anthrax nucleic acid, toxins, or antibodies can also sometimes be detected.[6,8] Lumbar puncture should be performed in the setting of meningeal signs and may demonstrate gross blood, numerous red blood cells, or xanthochromia.[6-8,10,11]

Treatment. Isolated cutaneous anthrax is typically treated with either oral ciprofloxacin or doxycycline.[6,8] Systemic anthrax with suspected meningitis is typically treated with ciprofloxacin, meropenem, and linezolid, or other triple antibiotic combinations.[6,8,9] Antitoxins may also be available.[12] For those at higher risk of exposure (eg, certain laboratory, animal, and military workers), a preexposure vaccine is available.[6-8] Oral antibiotics (eg, oral ciprofloxacin or doxycycline) and/or a vaccine may be recommended for postexposure prophylaxis.[6-9] Of note, while naturally occurring anthrax is sensitive to many types of antibiotics, bioengineered forms may be highly resistant.

Botulism

Cause. *Clostridium botulinum* is a gram-positive, anaerobic, spore-forming, bacillus bacteria found in soil that produces a highly potent neurotoxin.[13-17] Each of the 7 botulinum neurotoxin serotypes cleaves a specific protein in presynaptic peripheral neurons, preventing acetylcholine (ACh) vesicles from releasing their contents into the neuromuscular junction. The result is diffuse muscular weakness and possible respiratory failure, a clinical syndrome known as botulism.[13,14,16,18] Botulism is associated with significant mortality if untreated, and a single gram of crystallized toxin has the potential to kill more than a million people.[15,17] Although botulism is typically acquired through ingestion of contaminated food products (foodborne botulism) or contamination of wounds (wound botulism), the purified form of the toxin has the potential to be weaponized and disseminated as an aerosolized powder.[13-17]

Clinical presentation. The hallmark of botulism is a symmetric descending paralysis, starting with bilateral cranial nerve dysfunction and spreading caudally to include extremity and respiratory muscle weakness.[13-17] Mental status is usually preserved, as are reflexes until the extremity is severely weak. If the exposure is from ingestion, gastrointestinal symptoms (eg, nausea, vomiting, diarrhea, and/or constipation) may begin first, followed by neurologic symptoms within hours. Respiratory failure is the most common cause of death in the absence of mechanical ventilation. Autonomic symptoms may also occur. Botulism may be initially mistaken for myasthenia gravis, tick paralysis, or the Miller Fisher (or Fisher) variant of Guillain-Barré syndrome.[16]

Diagnosis. The initial diagnosis of botulism is usually made clinically, based on history and the classic descending paralysis.[13,16] Diagnosis is classically made by mouse bioassay (where suspected infectious material is injected into mice to see if they develop botulism), but the neurotoxin can sometimes also be identified by enzyme-linked immunosorbent assay tests.[13,16,19] Anaerobic culture to detect *C botulinum* or nucleic acid tests to detect its neurotoxin gene can also be considered. Although not definitive, electrodiagnostic studies may reveal reduced compound muscle action potential amplitudes (with preserved conduction velocity) and a small amplitude increment with high-frequency repetitive stimulation.[13] All *C botulinum*-specific laboratory testing should be performed under the direction of state or local health departments.[13,14,16]

Treatment. First, respiratory status should be assessed, and intubation with mechanical ventilation should be considered in the cases of impending respiratory failure. If botulism is suspected, clinicians should immediately call their state health department or the CDC regarding possible empiric administration of botulinum antitoxin for adults, or human-derived botulinum immunoglobulin (BabyBIG) for infants, which may limit further neurotoxin damage and progression.[13-18] Treatment should not wait for laboratory confirmation. Hypersensitivity reactions may occur. To minimize additional exposures, the patient's exposed skin should be washed with soap and water, and contaminated material/surfaces should be cleaned or discarded as appropriate.[13] Human-to-human transmission is not likely, and standard precautions are thought to be adequate. Recovery from botulism may take many months, but with adequate critical care support the mortality rate is now approximately 5%.[13,16]

Brucellosis

Cause. *Brucella* subspecies are ubiquitous gram-negative coccobacilli bacteria mostly affecting livestock.[20,21] Transmission to humans mainly occurs from consuming unpasteurized dairy products, eating undercooked meat, or being in close contact with infected animals, although inhalation is possible.[21] Human-to-human spread is rare, though transmission through sexual intercourse and breast feeding has been reported.[21] Brucella is a potentially attractive biological weapon because certain species are easy to aerosolize and are highly infectious, even at low doses.[21,22]

Clinical presentation. Symptoms of brucellosis begin 5 days to 5 months after exposure and may vary greatly from person to person. Acutely, brucellosis may cause a nonspecific flu-like illness with intermittent fevers. Hepatomegaly, splenomegaly, peripheral arthritis, sacroiliitis, spondylodiskitis, scrotal swelling, endocarditis, lymphadenopathy, and miscarriage may also occur. Infection may become chronic, with some symptoms lasting weeks to months, and may even recur after resolution. Fortunately, death is rare. Brucellosis involves the nervous system in about 5% to 10% of cases.[20,21]

Neurobrucellosis may present as headache, meningitis, and/or meningoencephalitis.[20,21,23] Chronically, it may cause peripheral neuropathy, radiculopathy, or cranial nerve palsies. Optic neuritis, cerebellitis, ischemic strokes, and myelitis have also been reported.[20,23]

Diagnosis and treatment. Diagnosis can be made by isolating *Brucella* subspecies in blood, bone marrow, or cerebrospinal fluid cultures.[20,21] Serologic antibody testing may be performed with paired acute and convalescent blood samples, but negative serologic results do not necessarily rule out infection. Cerebrospinal fluid analysis may demonstrate lymphocytic pleocytosis, elevated protein, and hypoglycorrhachia.[23] Initial treatment includes doxycycline plus streptomycin for systemic brucellosis, or ceftriaxone, doxycycline, and rifampin for neurobrucellosis.[20]

Plague

Cause. Plague is caused by the gram-negative coccobacillus bacteria, *Yersinia pestis*, with 3 distinct syndromes: bubonic, septicemic, and pneumonic.[24,25] *Y pestis* is found throughout many parts of the world, including Africa, Asia, South America, and Western North America, and is maintained in an enzootic cycle between various rodents and fleas. Transmission to humans may occur by the bite from an infected flea, contact with contaminated tissue or animals, or via respiratory droplets. Plague has caused several major pandemics throughout the world over the past 2 millennia, with more recent outbreaks mainly occurring in parts of Africa.[24-27] Given its morbidity, mortality, and ease of transmission, *Y pestis* may potentially be weaponized, possibly in aerosolized form, causing outbreaks of pneumonic plague.[25,26,28] In fact, *Y pestis* may have been one of the first biological agents used as a weapon when diseased cadavers were hurled into the besieged Crimean city of Caffa in 1346.[27]

Clinical presentation. Plague's syndromic manifestation and clinical presentation depends on the mode of transmission.[24-26,28] Bubonic plague, typically acquired through flea bites, is characterized by fevers, chills, and swollen painful lymph nodes (ie, buboes) in the cervical, axillary, and/or inguinal areas. Septicemic plague, either from untreated bubonic plague, flea bite, or contact with an infected animal, is characterized by fevers, chills, fatigue, abdominal pain, septic shock, and/or gangrenous extremities (which may have led to the term "black death"). Pneumonic plague, characterized by severe pneumonia, hemoptysis, respiratory failure, and/or septic shock, is acquired either though inhalation of infectious cough droplets or from progression of untreated bubonic or septicemic plague. Rarely, *Y pestis* can also seed the CNS, causing a meningoencephalitis in <10% of plague cases with fever, headache, meningismus, and altered mental status.[25,26] With proper treatment, the mortality rate of all plague forms is estimated to be around 10%, though is higher with the septicemic and pneumonic forms.[24,25]

Diagnosis. *Y pestis* can usually be identified by gram stain or culture of preantibiotic blood, sputum, cerebrospinal fluid, and/or lymph node aspirate samples.[24,25] Serologic antibody tests are also available, ideally using both acute and convalescent serum samples. Evidence of *Y pestis* in tissues can sometimes be found by nucleic acid tests. Cerebrospinal fluid may demonstrate a neutrophilic pleocytosis in those with plague meningoencephalitis.[25]

Treatment. Untreated plague has high mortality.[24,25] Any suspected pneumonic plague cases should be isolated and put on droplet precautions immediately. Intravenous (IV) gentamicin or fluoroquinolone antibiotics should be started quickly, with transition to oral versions only after clinical improvement. Streptomycin, doxycycline, and chloramphenicol have also been used as alternatives. Close contacts or exposed individuals should receive prophylaxis for 7 days with oral doxycycline or a fluoroquinolone.[24-26]

Smallpox

Cause. Smallpox, which was declared eradicated from global circulation in 1980, is caused by the variola virus, a large double-stranded DNA virus in the *orthopoxvirus* viral genus.[29-32] The virus is transmitted from human to human mainly by airborne droplets of saliva from an infected person, and less so from contact with smallpox vesicles or scabs. It is so highly transmissible that smallpox incidence among close household contacts is estimated to be 60%. Historically, smallpox has been used as a biologic weapon, including the British during the French and Indian Wars.[31] Although all remaining variola virus has been restricted to 2 government research laboratories in the United States and Russia, it is suspected that unsanctioned reserves may exist elsewhere. Given that the variola virus is easily aerosolized, infectious at low doses, and highly transmissible, it can be an ideal bioterrorism agent.[29,31] This is especially true given that smallpox vaccinations (ie, live vaccinia virus inoculation) have not been routinely administered since 1980 except to military personnel, leaving much of the current population susceptible.

Clinical presentation. Historically, symptoms of smallpox begin after an incubation period of 1 to 2 weeks. It generally starts with a high fever, delirium, hallucinations, headache, backache, myalgia, abdominal pain, and/or fatigue.[29-31] Skin lesions then develop in the oropharynx and spread to the face, trunk, extremities, palms, and soles. The skin lesions uniformly evolve from macules to vesicles to the characteristic umbilicated pustules, which eventually form an eschar and scar if the patient survives. Mortality rates are proportional to the area of skin involved and are as high as 75%.[30] Rarely,

smallpox can become diffusely hemorrhagic, usually resulting in death. Smallpox sometimes causes a meningoencephalitis or blindness from corneal scarring. Finally, vaccination against smallpox using the vaccinia virus also rarely results in serious clinical symptoms, including disseminated rash, encephalitis, or acute disseminated/demyelinating encephalomyelitis.[29,30,32]

Diagnosis. Initial diagnosis of smallpox is clinical with the 3 major criteria being (1) a febrile prodrome with (2) diffuse vesicles or pustules that are (3) all in the same stage of development (eg, all vesicles or all pustules), and may affect the palms and soles.[29] Anyone suspected of having smallpox should be immediately isolated using airborne precautions, and the local and state health department should be contacted promptly. The CDC can confirm infection by isolating the variola virus or detecting nucleic acid in samples. Differential diagnosis for smallpox may include varicella/chickenpox, disseminated herpes zoster or herpes simplex, drug eruptions, or disseminated vaccinia from the smallpox vaccine.[29,30]

Treatment. There is no proven disease-modifying treatment for smallpox, though there are 3 antiviral therapies that have experimental anti-orthopoxvirus activity: vaccinia immune globulin IV, tecovirimat/ST-246, and cidofovir.[29] Smallpox vaccination with vaccinia virus may prevent or lessen severity of disease if given within 2 to 3 days of initial exposure. The CDC should be consulted for treatment recommendations.

Chemical Agents

Organophosphates and Nerve Agents

Mechanism. Organophosphorus (OP) agents, which include both pesticides and the more potent nerve agents, inhibit all cholinesterases, most importantly acetylcholinesterase (AChE) found in neuronal synapses. This leads to an excess of ACh at both the nicotinic and muscarinic postsynaptic receptors.[33] The OP competitively inactivates AChE by binding to the active site which normally binds to and cleaves ACh. If this binding is not reversed, "aging" will occur in which the OP–AChE complex, and thus enzyme inactivation, becomes permanent.[34,35]

Clinical presentation. Acute neurologic effects from OP exposure vary based on the agent, dose, and route of exposure, and affect both the central and peripheral nervous systems. Central nervous system effects can include anxiety and restlessness, CNS depression ranging from mild somnolence to coma, direct inhibition of respiratory centers, and seizures. Seizures are relatively common with nerve agents, but less common with pesticide exposures.[35] The most common muscarinic and nicotinic effects are summarized in Table 2. Additionally, muscarinic stimulation can cause rhinorrhea and laryngeal spasm, and nicotinic stimulation can also cause weakness of the tongue and pharynx, leading to upper airway obstruction. Opsoclonus, ocular bobbing, and choreoathetosis are rare findings. Cardiac effects will usually begin with tachycardia from nicotinic stimulation, followed by bradycardia and various heart blocks due to muscarinic stimulation, and ultimately can deteriorate into QTc prolongation, ventricular irritability, dysrhythmias, and sudden cardiac death.[36] When death does occur, it is usually from respiratory or cardiac arrest.[4,35,37-39] Pediatric patients will typically present with a predominance of CNS effects.[40,41]

Table 2. Common Muscarinic and Nicotinic Effects of Organophosphates and Nerve Agents.

Muscarinic Effects (DUMBBBELS)	Nicotinic Effects (MTWThFS)
Diarrhea	Mydriasis/Muscle Cramps
Urination	Tremor/Twitching
Miosis	Weakness
Bronchorrhea/Bronchospasm/Bradycardia	Tachycardia
Emesis	Fasciculations
Lacrimation	Seizures
Salivation	

Intermediate syndrome (IS), the etiology of which is unclear, is a cluster of delayed neurologic symptoms manifesting 24 to 96 hours after exposure and lasting 2 to 40 days. It usually begins with weakness of the neck flexors and cranial nerve palsies and then progresses to the proximal musculature, including the respiratory muscles. Treatment is supportive and prolonged mechanical ventilation is often required. Unfortunately, OP antidotes have not been shown to be effective at treating or preventing IS.[35,36,42]

Diagnosis. Diagnosis of OP poisoning is primarily clinical. Standard laboratory tests are often normal or nonspecific, and surrogate markers for AChE are limited by false positives, slow result times, and a lack of clinical correlation to the actual AChE level.[35,43] Electromyography/nerve conduction studies may or may not be abnormal in acute exposure and may not correlate with clinical symptoms.[44]

Treatment. Early airway management is often necessary, and since succinylcholine is metabolized by a cholinesterase, a nondepolarizing paralytic should be used for intubation.[45] Seizures should be treated with benzodiazepines, ideally one with long duration of action. The mainstay of OP treatment is muscarinic blockade with atropine. The starting dose is 1 to 2 mg IV, which can be doubled every 5 minutes with the end point of drying respiratory secretions. In severe poisonings, total doses of multiple *grams* have been required. Nicotinic symptoms are not reversed with atropine and should not be used as an end point for therapy.[35,36,39,43,46,47] Oximes, such as pralidoxime chloride (2-pyridine aldoxime methyl chloride [2-PAM]), can reactivate bound AChE if given prior to aging

and should be given as soon as OP poisoning is strongly suspected.[35] The federal government has created and strategically placed large stockpiles of diazepam, atropine, and 2-PAM (known as "ChemPacks") throughout the United States in preparation of potential mass-casualty incidents. The CDC or local poison center can assist in accessing these resources.[39]

Cyanide

Mechanism. Cyanide's primary mechanism of action is to inhibit the electron transport chain, preventing the utilization of oxygen and the formation of adenosine triphosphate.[48,49] Cyanide has also been shown to directly activate NMDA receptors and indirectly enhance their activity. This increases intracellular calcium, leading to reactive oxygen species which cause lipid peroxidation, neuronal apoptosis, and neurodegeneration.[48,50,51]

Clinical presentation. Effects of cyanide poisoning are apparent within seconds of inhalation and minutes of ingestion.[52] Early signs are unfortunately nonspecific and mimic those of acute hypoxia, such as tachypnea and hyperpnea.[53] Neurologic signs include headache, anxiety, agitation, and giddiness, followed by confusion and lethargy. Blurred vision may result from mydriasis. The patient's skin may have a red hue from decreased oxygen usage, although this finding is rare and is best seen in the vessels of the retina.[48] There may be an initial compensatory tachycardia and hypertension followed by vasodilation, decreased inotropy, hypotension, bradycardia, and cardiac arrest.[48,53] Ultimately, the patient may experience seizures, coma, and death.[48,53,54] Survivors may develop parkinsonism as a result of damage to the basal ganglia, though it is unclear if this is due to direct damage from cyanide or a result from secondary hypoxia.[48]

Diagnosis. Diagnosis of cyanide poisoning is based primarily on history; however, lab testing may aid in the diagnosis. Patients will have a significantly elevated anion gap and a significantly elevated lactate.[48,55,56] A serum lactate level >8 mmol/L has been found to be 94% sensitive and 70% specific for toxic blood cyanide levels in the appropriate clinical setting.[56] A difference in SaO_2 and SvO_2 on blood gas analysis of <10% is also sensitive (but not specific) for cyanide poisoning. Direct testing of blood cyanide is available for confirmation but will not result quickly enough to guide therapy.[48,55,57,58]

Treatment. Shock and hypotension should be treated with IV fluids and vasopressors. Sodium bicarbonate may be given for severe acidemia.[48,59] While activated charcoal only weakly adsorbs cyanide, even this weak effect may be beneficial to patient survival.[48]

Antidote treatment should be initiated empirically once poisoning is suspected.[48,59] The preferred antidote is hydroxocobalamin (vitamin B_{12a}, administered as a highly concentrated 5 g IV infusion of a 25 mg/mL solution). Hydroxocobalamin binds cyanide forming nontoxic cyanocobalamin (vitamin B_{12}), which is then renally excreted. Although rarely utilized, the older cyanide antidote kit may still be found consisting of amyl nitrite, sodium nitrite, and sodium thiosulfate. The nitrites induce methemoglobinemia, for which cyanide has a greater affinity than it does hemoglobin.[60] Sodium thiosulfate then helps catalyze the metabolism of cyanide to nontoxic thiocyanate, which is eliminated. Nitrites should be avoided if a concomitant carbon monoxide exposure or a preexisting methemoglobinemia is suspected (eg, smoke inhalation) as the nitrite-induced methemoglobinemia could worsen the patient's already impaired oxygen carrying capacity.[59,61] Hydroxocobalamin, however, appears to be a more effective, safer, and faster antidote than the cyanide antidote kit.[59,62,63] There is no clear benefit of combining thiosulfate and hydroxocobalamin.[52]

Carfentanil

Mechanism. Carfentanil, a derivative of fentanyl, is an ultrapotent opioid roughly 10 000× more potent than morphine and represents one of the newer potential terrorist agents.[64] It has recently lead to a growing number of fatalities among drug users and secondary exposures to first responders.[65] As an opioid, carfentanil stimulates the mu ($\mu_1$and μ_2) and possibly delta (δ) receptors in the brain, causing CNS, respiratory, and cardiac depression.

Clinical presentation. Death from opioid overdose is almost always the result of respiratory failure. Stimulation of the μ_2 and δ receptors in the medulla decreases both respiratory rate and tidal volume, as well as the chemoreceptor response to hypercarbia in the carotid and aortic bodies.[66] Other, nonpulmonary, effects include CNS depression, mild decrease in blood pressure, nausea, vomiting, constipation, hypopituitarism, adrenal insufficiency, and hearing loss.[67] Seizures resulting from carfentanil toxicity are thought to be the result of profound hypoxia.[67]

Diagnosis. Diagnosis of an opioid overdose should be clinical. Although there are specific assays for various ultrapotent agents, these are not generally available in time to make a clinical decision.[64,65] The potential cross-reactivity of carfentanil with the fentanyl immunoassay used in urine drug screens (UDSs) is not well known, so a negative UDS may or may not rule out an exposure.

Treatment. Since the primary cause of morbidity and mortality in opioid overdoses is respiratory failure, early airway management and oxygenation is the priority accompanied with opioid antagonist (OA) administration.[67] The OAs work by competitively inhibiting μ receptors, reversing the effects of opioids in a dose-dependent manner.[67] Current recommendations are to empirically treat any patient with undifferentiated

CNS and respiratory depression with a starting dose of 0.04 mg IV naloxone and escalating the dose every 2 to 3 minutes if no response, to 0.4, 2, and 10 mg.[67,68] The goal is not reversal of CNS depression, but rather improvement in oxygenation and ventilation. If 10 mg has been reached with no response, it is less likely that an opioid is responsible, and standard supportive management should continue.[67] In a mass-casualty setting, in which time and resources are limited and concern for withdrawal is low (such as in a terrorist attack), it is reasonable to consider starting with higher doses. Opioid half-life is typically longer than OA duration of action; therefore, patients should be monitored and redosed as needed. Of note, no studies to date show that higher dosages of naloxone are recommended for reversal of ultrahigh-potency fentanyl analogs compared to other opiates because of a potential ceiling effect.

Summary and Recommendations

There are numerous biological and chemical agents that could intentionally be used against a population (many of which are not listed here), and several can cause various neurologic syndromes (Table 2). Such agents of "neuroterrorism" may cause nonspecific symptoms initially, making diagnosis difficult.[5] An epidemiologic clue to the use of such agents would include abnormal temporal and/or geographic clustering of patients with similar clinical syndromes. Neurohospitalists should be on the lookout for such abnormal clustering, especially among patients presenting to the emergency department. If use of such an agent is suspected, the neurohospitalist should immediately consult with emergency department personnel, infection control, infectious disease physicians, and/or Poison Control (800-222-1222) to make sure the scene is safe and to stabilize and isolate patients if necessary. The neurohospitalist should also immediately contact their local and/or state health department to report their suspicion and to obtain guidance and assistance. If the local and/or state health department is not available, the neurohospitalist can alternatively call the CDC Emergency Operations Center (770-488-7100). As guidelines are frequently updated, please check the latest local and/or national (CDC) emergency management guidelines for any of the above conditions for the most up-to-date information.

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