Chapter 5

INCAPACITATING AGENTS

Summary

NATO Code: BZ

Signs and Symptoms: Mydriasis; dry mouth; dry skin; increased deep tendon reflexes; decreased level of consciousness; confusion; disorientation; disturbances in perception and interpretation (illusions and/or hallucinations); denial of illness; short attention span; impaired memory.

Field Detection: No field detector is available.

Decontamination: Gentle but thorough flushing of skin and hair with water or soap and water is all that is required. Remove clothing.

Management: *Antidote:* physostigmine. *Supportive:* monitoring of vital signs, especially core temperature.

Overview

BZ, or 3-quinuclidinyl benzilate, is a glycolate anticholinergic compound dispersed as an aerosolized solid when intended for inhalation, or as agent dissolved in one or more solvents when intended for ingestion or percutaneous absorption. Acting as a competitive inhibitor of acetylcholine at postsynaptic and postjunctional muscarinic receptor sites, BZ causes peripheral nervous system (PNS) effects that in general are the opposite of those seen in nerve agent poisoning. Central nervous system

(CNS) effects include stupor, confusion, and confabulation with concrete and panoramic illusions and hallucinations, and with regression to automatic "phantom" behaviors such as plucking and disrobing. The combination of anticholinergic PNS and CNS effects aids in the diagnosis of patients exposed to these agents. Physostigmine, which increases the concentration of acetylcholine in synapses and in neuromuscular and neuroglandular junctions, is a specific antidote.

History and Military Relevance

The use of chemicals to induce altered states of mind dates to antiquity and includes the use of plants such as thorn apple (*Datura stramonium*) that contain combinations of anticholinergic alkaloids. The use of nonlethal chemicals to render an enemy force incapable of fighting dates back to ancient Greece, where, according to some accounts, in 600 BCE Solon's soldiers threw hellebore roots into streams supplying water to enemy troops, who then developed diarrhea. In 184 BCE Hannibal's army used belladonna plants to induce disorientation, and in AD 1672 the Bishop of Muenster attempted to use belladonna-containing grenades in an assault on the city of Groningen. In 1881, members of a railway surveying expedition crossing Tuareg territory in North Africa ate dried dates that tribesmen had apparently deliberately contaminated with *Hyoscyamus falezlez*, causing intoxication, excruciating pain, weakness, and unintelligible speech. In 1908, 200 French soldiers in Hanoi became delirious and experienced hallucinations after being poisoned with a related plant. More recently, Soviet use of incapacitating agents internally and in Afghanistan was alleged, but never substantiated.

Following World War II, the US military investigated a wide range of possible nonlethal, psychobehavioral, chemical incapacitating agents including psychedelic indoles such as lysergic acid diethylamide (LSD-25) and marijuana derivatives, certain tranquilizers, and several glycolate anticholinergics. BZ was one of the anticholinergic compounds. It was weaponized beginning in the 1960s for possible battlefield use. Although BZ figured prominently in the plot of the 1990 movie *Jacob's Ladder* as

the compound responsible for hallucinations and violent deaths in a fictitious American battalion in Vietnam, this agent never saw operational use. Destruction of American stockpiles began in 1988 and is now complete.

In February 1998, the British Ministry of Defence released an intelligence report that accused Iraq of having stockpiled large amounts of a glycolate anticholinergic incapacitating agent known as Agent 15. This compound is speculated either to be identical to BZ or a closely related derivative. Also in 1998, there were allegations that elements of the Yugoslav People's Army used incapacitating agents that caused hallucinations and irrational behavior against fleeing Bosnian refugees. Physical evidence of BZ use in Bosnia remains elusive, however.

Nomenclature

The term "incapacitation," when used in a general sense, is roughly equivalent to the term "disability" as used in occupational medicine and denotes the inability to perform a task because of a quantifiable physical or mental impairment. In this sense, any of the chemical warfare agents may incapacitate a victim; however, again by the military definition of this type of agent, incapacitation refers to impairments that are temporary and nonlethal. Thus, riot-control agents are incapacitating because they cause temporary loss of vision due to blepharospasm, but they are not considered military incapacitants because the loss of vision does not last long.

Although incapacitation may result from physiological changes such as mucous membrane irritation, diarrhea, or hyperthermia, the term "incapacitating agent" as militarily defined refers to a compound that produces temporary and nonlethal impairment of military performance by virtue of its psychobehavioral or CNS effects.

Nonmilitary Sources

BZ and related anticholinergic compounds can be synthesized in clandestine laboratories, but their illicit use is uncommon, possibly because of some unpleasant effects such as dry mouth

and skin. The anticholinergics atropine, oxybutynin, and scopolamine find use in clinical medicine and are available as pharmaceuticals, as are antihistamines that have prominent anticholinergic side effects. BZ is widely used in pharmacology as a muscarinic receptor marker. As mentioned above, anticholinergic hallucinogenic compounds are present in thorn apple as well as other plants of the family *Solanaceae*, which also includes black henbane (*Hyoscyamus niger*), belladonna (or deadly nightshade, *Atropa belladonna*), woody nightshade (*Solanum dulcamara*), and Jerusalem cherry (*Solanum pseudocapsicum*). These plants contain varying proportions of the anticholinergic glycolates atropine, hyoscyamine, and hyoscine.

Physiochemical Characteristics

BZ is odorless. It is stable in most solvents, with a half-life of 3 to 4 weeks in moist air; even heat-producing munitions can disperse it. It is extremely persistent in soil and water and on most surfaces. It is also soluble in propylene glycol, dimethyl sulfoxide, and other solvents. Agent 15 presumably shares many of the physiochemical properties of BZ.

Detection and Protection

Because BZ is odorless and nonirritating, and because clinical effects are not seen until after a latent period of 30 minutes to 24 hours, exposure could occur without the knowledge of casualties. No currently available field military or civilian detector is designed to disclose the presence of BZ or other anticholinergic compounds in the environment. Confirmation of the exact chemical involved in an incapacitating agent exposure requires laboratory analysis of environmental specimens containing the agent. The high-efficiency particulate air (HEPA) filter in the canister of the chemical protective mask prevents exposure of the face and respiratory tract to aerosolized BZ. The chemical protective ensemble protects the skin against contact with BZ or other incapacitating agents dispersed as fine solid particles or in solution. Protection against ingestion would depend upon a high index of suspicion for BZ-contaminated food or drink.

Toxicokinetics

Bioavailability of BZ via ingestion and by inhalation of 1-μm particles approximates 80% and 40% to 50%, respectively. Percutaneous absorption of BZ dissolved in propylene glycol yields, after a latent period of up to 24 hours, serum levels approximately 5% to 10% of those achieved with intravenous (IV) or intramuscular (IM) administration. Although inhalation of aerosolized BZ is probably the greatest risk on the battlefield, terrorists may choose to disseminate BZ in forms that provide significant opportunities for ingestion and absorption through the skin.

Following absorption, BZ is systemically distributed to most organs and tissues of the body. Its ability to reach synapses and neuromuscular and neuroglandular junctions throughout the body is responsible for its PNS effects, whereas its ability to cross the blood-brain barrier is responsible for its CNS effects. Atropine and hyoscyamine both cross the placenta and can be found in small quantities in breast milk; whether this is also true for BZ is unclear. Metabolism of BZ occurs primarily in the liver, with elimination of unchanged agent and metabolites chiefly in the urine.

Toxicity

The characteristic that makes BZ and other glycolates an incapacitating rather than a toxic chemical warfare agent is its high safety ratio. The amount required to produce effects is a thousand or more times less than a fatal dose of the compound. The ICt_{50} (the concentration-time product needed to produce incapacitation in 50% of an exposed group) for BZ is 112 mg•min/m^3, whereas the LCt_{50} (median lethal concentration) is estimated to be almost 2,000 times the dose needed for incapacitation.

Mechanism of Action

The agent BZ and other anticholinergic glycolates act as competitive inhibitors of the neurotransmitter acetylcholine neurons at two places: (1) postjunctional muscarinic receptors in cardiac and smooth muscle and in exocrine (ducted) glands

and (2) postsynaptic receptors in neurons. As the concentration of BZ at these sites increases, the proportion of receptors available for binding to acetylcholine decreases, and the end organ "sees" less acetylcholine. (One way of visualizing this process is to imagine BZ coating the surface of the end organ and preventing acetylcholine from reaching its receptors.) Because BZ has little to no agonist activity with respect to acetylcholine, high concentrations of BZ essentially block acetylcholine at these sites, leading to clinical effects reflective of understimulation of end organs.

Clinical Effects

Peripheral Effects

- Mydriasis, blurred vision
- Dry mouth, dry skin
- Initially rapid heart rate; later, normal or slow heart rate
- Possible atropine flush

The PNS effects of BZ are, in general, readily understood as those of understimulation of end organs and are qualitatively similar to those of atropine. Due to PNS effects, patients have been described as "dry as a bone, hot as a hare, red as a beet, and blind as a bat." Decreased stimulation of eccrine and apocrine sweat glands in the skin results in dry skin and a reduction in the ability to dissipate heat by evaporative cooling. The skin becomes warm partly from decreased sweating and partly from compensatory cutaneous vasodilatation (the skin becomes red, with a so-called atropine flush) as the body attempts to shunt a higher proportion of core-temperature blood as close as possible to the surface of the skin. With heat loss decreased, the core temperature itself rises. Understimulation of other exocrine glands leads to dry mouth, thirst, and decreased secretions from lacrimal, nasal, bronchial, and gastrointestinal glands.

Decreased cholinergic stimulation of pupillary sphincter muscles allows α-adrenergically innervated pupillary dilating muscles to act essentially unopposed, resulting in mydriasis.

(In fact, the cosmetic effect of mydriasis in women who applied extracts of deadly nightshade topically to their eyes explains the name "belladonna" [beautiful lady] given to this plant.) Similar effects on cholinergic ciliary muscles produce paralysis of accommodation. Other smooth muscle effects from BZ intoxication include decreased bladder tone and decreased urinary force with possibly severe bladder distention.

Typically BZ initially raises the heart rate, but hours later, depending on the dose of BZ, the heart rate returns to baseline or may become bradycardic. Either the peripheral vagal blockade has ceased, or the stimulation of the vagal nucleus has occurred.

Neither atropine nor BZ can act directly at the postjunctional nicotinic receptors found in skeletal muscle, but BZ-exposed patients nonetheless exhibit muscle weakness. This weakness, along with incoordination, heightened stretch reflexes, and ataxia, is probably due to the effects of BZ at CNS sites.

Central Effects

- Disturbances in level of consciousness
- Misperceptions and difficulty in interpretation (delusions, hallucinations)
- Poor judgment and insight (illness denial)
- Short attention span, distractibility, impaired memory (particularly recent)
- Slurred speech, perseveration
- Disorientation
- Ataxia
- Variability (quiet/restless)

The PNS effects of BZ are essentially side effects that are useful in diagnosis but incidental to the CNS effects for which the incapacitating agents were developed. These CNS effects include a dose-dependent decrease in the level of consciousness, beginning with drowsiness and progressing through sedation to stupor and coma. The patient is often disoriented to time and place. Disturbances in judgment and insight occur. The patient may abandon socially imposed restraints and resort to

vulgar and inappropriate behavior. Perceptual clues may no longer be readily interpretable. The patient is easily distracted and may have memory loss, most notably short-term memory. In the face of these deficits, patients try to make sense of their environment and will not hesitate to make up answers on the spot to questions that confuse them. Speech becomes slurred and often senseless, and loss of inflection produces a flat, monotonous voice. References become concrete and semiautomatic, with colloquialisms, clichés, profanity, and perseveration. Handwriting also deteriorates. Semiautomatic behavior may also include disrobing (perhaps partly because of increased body temperature), mumbling, and phantom behaviors such as constant picking, plucking, or grasping motions ("woolgathering" or carphology).

CNS-mediated perceptual disturbances in BZ poisoning include both illusions (misidentification of real objects) and hallucinations (the perception of objects or attributes that have no objective reality). (Although the phrase "mad as a hatter" refers to poisoning from mercury formerly used by hatters on felt, it can just as well serve as a reminder of CNS effects from anticholinergics.) Anticholinergic hallucinations differ from the often vague, ineffable, and often transcendent-appearing hallucinations induced by hallucinogenic indoles such as LSD. Hallucinations from BZ tend to be realistic, distinct, easily identifiable (often commonly encountered objects or persons), and panoramic, and they usually become less extreme during the course of the intoxication.

Another prominent CNS finding in BZ poisoning is behavioral lability, with patients swinging back and forth between quiet confusion and self-absorption in hallucinations to frank combativeness. Moreover, as other symptoms begin to resolve, intermittent paranoia may be seen. Automatic behaviors common during resolution include the crawling or climbing motions called "progresso obstinato" in old descriptions of dementia.

BZ produces effects not just in individuals, but also in groups, with shared illusions and hallucinations (*folie à deux*, *folie en famille*, and "mass hysteria"). For example, two BZ-intoxicated individuals took turns smoking an imaginary cigarette clearly visible to both of them but to no one else.

Time Course of Effects

Clinical effects from ingestion or inhalation of BZ appear after an asymptomatic or latent period that may be as little as 30 minutes or as long as 24 hours; the usual range is 30 minutes to 4 hours, with a mean of 2 hours. However, effects may not appear up to 36 hours after skin exposure to BZ. Once effects appear, their duration is typically 72 to 96 hours and dose-dependent. Following an ICt_{50} of BZ, severe effects may last 36 hours, but mild effects may persist for an additional day.

The clinical course from BZ poisoning can be divided into the following four stages:

1. Onset or induction (0 to 4 hours after exposure), characterized by parasympathetic blockade and mild CNS effects.
2. Second phase (4 to 20 hours after exposure), characterized by stupor with ataxia and hyperthermia.
3. Third phase (20 to 96 hours after exposure), in which full-blown delirium is seen but often fluctuates from moment to moment.
4. Fourth phase, or resolution, characterized by paranoia, deep sleep, reawakening, crawling or climbing automatisms, and eventual reorientation.

Differential Diagnosis

The differential diagnosis for irrational and confused patients is a long one (Table 5-1) and includes anxiety reactions as well as intoxication with a variety of agents, including hallucinogenic indoles (such as LSD), cannabinoids (such as the δ-9-tetrahydrocannabinol in marijuana), lead, barbiturates, and bromides. All of these conditions can lead to restlessness, lightheadedness (with associated vertigo and ataxia), confusion, and erratic behavior, with or without vomiting. Clues that specifically point to BZ or a related compound are the combination of anticholinergic PNS effects ("dry as a bone, hot as a hare, red as a beet, and blind as a bat") with the CNS effects ("mad as a hatter") of slurred and monotonous speech, automatic behavior (perseveration, disrobing, and phantom

Table 5-1. Differential Diagnosis for Incapacitating Agent Exposure

Signs and Symptoms	Possible Etiology
Restlessness, dizziness, or giddiness; failure to obey orders, confusion, erratic behavior; stumbling or staggering; vomiting.	Anticholinergics, indoles (LSD), cannabinols, anxiety reaction, other intoxicants (alcohol, lead, bromides, barbiturates).
Dry mouth, tachycardia at rest, elevated temperature, facial flushing, blurred vision, pupillary dilation, slurred or nonsensical speech, hallucinatory behavior, disrobing, mumbling and picking behavior, stupor and coma.	Anticholinergics
Inappropriate smiling or laughter, irrational fear, difficulty expressing self, distractibility, perceptual distortions, labile increase in pupil size, increased heart rate and blood pressure, stomach cramps, vomiting.	Indoles (Schizophrenic psychosis may mimic these symptoms in some respects.)
Euphoric, relaxed, unconcerned attitude; daydreaming; easy laughter; hypotension and dizziness on sudden standing.	Cannabinols
Tremor, clinging or pleading, crying, clear answers, phobias, decrease in disturbance with reassurance, history of nervousness or immaturity.	Anxiety reaction

LSD: lysergic acid diethylamide

behaviors ["woolgathering"]), and vivid, realistic, describable hallucinations (decreasing in size over time) in a patient slipping into and out of delirium.

Atropine intoxication from autoinjector use in a patient not exposed to nerve agents may create similar PNS effects to those seen in BZ intoxication. However, marked confusion from atropine is not normally seen until a total of six or seven autoinjectors have been given (in a hot, dehydrated, or battle-stressed individual, less atropine would probably suffice). Circumstantial evidence may be helpful in differential diagnosis.

Heat stroke may also generate hot, dry, and confused or stuporous casualties and must be considered. Patients with anxiety reactions are usually oriented to time, place, and person but may be trembling, crying, or otherwise panicked. The classic picture of unconcern may characterize a patient with a conversion reaction, but these patients are also likely to be oriented and lack the anticholinergic PNS signs of BZ poisoning.

Medical Management

These guidelines for general patient care are not intended to take the place of sound clinical judgment, especially in the management of complicated cases. The admonition to protect oneself first may be difficult when dealing with any intoxication involving a latent period, since healthcare providers may already have been exposed during the same time frame as patients. Protection of medical staff from BZ that has already been absorbed and systemically distributed in a patient is not needed.

General supportive management of the patient includes decontamination of skin and clothing (ineffective for agent that has already been absorbed but useful in preventing further absorption of any agent still in contact with the patient), confiscation of weapons and related items from the patient, and observation. Physical restraint may be required in moderately to severely affected patients. The greatest risks to the patient's life are (*a*) injuries from his or her own erratic behavior (or from the behavior of similarly intoxicated patients) and (*b*) hyperthermia, especially in patients who are in hot or humid environments or are dehydrated from overexertion or insufficient water intake. A severely exposed patient may be comatose with serious cardiac arrhythmias and electrolyte disturbances. Managing heat stress is a high priority in these patients. Because of the prolonged time course in BZ poisoning, consideration should always be given to evacuation to a higher care level.

Because BZ effectively decreases the amount of acetylcholine "seen" by postsynaptic and postjunctional receptors, specific antidotal therapy in BZ poisoning is geared toward raising the concentration of acetylcholine in these synapses and

junctions. Any compound that causes a rise in acetylcholine concentration can potentially overcome BZ-induced inhibition and restore normal functioning; even the nerve agent VX has been shown to be effective when given under carefully controlled conditions. The specific antidote of choice in BZ poisoning is the carbamate anticholinesterase physostigmine, which temporarily raises acetylcholine concentrations by binding reversibly to anticholinesterase on the postsynaptic or postjunctional membrane. Physostigmine is similar in many ways to pyridostigmine and is equally effective when used as a preexposure antidotal enhancer (pretreatment) in individuals at high risk for subsequently encountering soman. However, physostigmine is not used for this purpose because the doses required cause vomiting through CNS mechanisms. In the case of BZ poisoning, a nonpolar compound such as physostigmine is used specifically because penetration into the brain is required in those individuals who already have CNS effects from BZ.

In BZ-intoxicated patients, physostigmine is minimally effective during the first 4 hours after exposure but is very effective after 4 hours. Oral dosing generally requires one and a half times the amount of antidote as does IM or IV administration. However, effects from a single intramuscular injection of physostigmine last only about 60 minutes, necessitating frequent re-dosing. It must be emphasized that physostigmine does not shorten the clinical course of BZ poisoning and that relapses will occur if treatment is discontinued prematurely. The temptation to substitute a slow IV infusion for IM injections should be tempered by the awareness that IV infusion may lead to bradycardia (similar to that caused by nerve agents), and too rapid infusion can cause arrhythmias, excessive secretions (to the point of compromising air exchange), and convulsions. Moreover, the sodium bisulfite in commercially available preparations of physostigmine may cause life-threatening allergic responses.

Suggested Dosages of Physostigmine

- **Test dose.** If the diagnosis is in doubt, a dose of 1 mg may be given. If a slight improvement occurs, routine dosing should be given.

- **Routine dosing.** Adult doses of about 45 μg/kg have been recommended, which may be modified by the response. A mental status examination should be done every hour, and the dose and time interval of dosing should be modified according to whether or not mental status is improved. As the patient improves, the dosage requirement will decrease. Oral dosing is the preferred route after the initial IV dose. This will decrease the risk of overdose that could be created by further IV administration.
- **Routes of administration**. For each route, titrate about every 60 minutes to mental status.
  - IM: 45 μg/kg in adults (20 mg/kg in children)
  - IV: 30 μg/kg slowly (1 mg/min)
  - PO (by mouth): 60 μg/kg if patient is cooperative (because of bitter taste, consider diluting in juice)

History and Toxicity of Physostigmine

The antagonism between physostigmine (derived from the calabar bean) and atropine (tincture of belladonna) was first reported in 1864 by a physician who successfully treated prisoners who had become delirious after drinking tincture of belladonna. Physicians did not notice this report until the 1950s, when atropine coma (in which 50 mg or so of atropine was given to certain psychiatric patients) was successfully treated with physostigmine after the "therapeutic benefit" had been attained. Again, this went unnoticed until a controlled study reported in 1967 indicated that anticholinergic intoxication could be successfully, albeit transiently, reversed by physostigmine.

The administration of physostigmine by the IV route in a delirious but conscious and otherwise healthy patient is not without peril. It is sometimes difficult to keep a delirious patient quiet long enough to administer the drug. Even if administered correctly (very slowly), the heart rate may decline from 110 to 45 beats per minute over a period of 1 to 2 minutes. The difference in the onset of the effects after IM and IV administration of physostigmine is a matter of only several minutes. Since its use is rarely lifesaving, this slight difference in time of response is inconsequential. Refer to the product insert for dosage and administration.

Physostigmine is a safe and effective antidote if used properly. In a conscious and delirious patient it will produce very effective but transient reversal of both the peripheral and central effects of cholinergic-blocking compounds. Its use by the IV route is not without hazards. It should NOT be used in a patient with cardiorespiratory compromise, hypoxia, or acid-base imbalance with a history of seizure disorders or arrhythmias.

Triage

A casualty with cardiorespiratory compromise or severe hyperthermia should be considered *immediate*. Casualties in this condition are possible, though unlikely. Immediate attention to ventilation, hemodynamic status, and temperature control may be lifesaving. Because of its dangers in a hypoxic or hemodynamically challenged patient, physostigmine should be considered a second-line management option to be used only if adequate attention can simultaneously be given to temperature and other vital signs.

A casualty with pronounced or worsening anticholinergic signs should be triaged as *delayed*, and physostigmine should be considered.

A casualty with mild PNS or CNS anticholinergic effects may be considered *minimal*. Given the time course of BZ intoxication, however, these patients should not be considered able to manage themselves or capable of routine return to duty, and should be relieved of their weapons, observed, and if the holding capacity at the current role is exceeded, evacuated.

A casualty with severe cardiorespiratory compromise when treatment or evacuation resources are insufficient may be considered *expectant*; however, patients in this condition are also unlikely.

Return to Duty

Given the time course of the intoxication, early return to duty is probably not a realistic possibility for the majority of casualties, who may require observation and management for at least several days.