

BOTULINUM TOXIN: FROM BOTOX TO BIOTERRORISM

LAST SUMMER a 47-year-old man presented to a local hospital with a 48-hour history of proximal muscle weakness and descending paralysis. Illness progressed, and the patient was put on a ventilator. No recent GI illness was reported, but history included both alcohol and injection-drug use. Although the patient had no obvious wounds, wound botulism was first in the differential. Oregon Health Services was called, and antitoxin was ordered. Mouse bioassay of patient serum by the Oregon State Public Health Lab revealed botulinum toxin type A.

Botulinum toxin is a remarkable substance. What else promises the look of eternal youth* and yet is considered the most poisonous substance known?¹ This *CD Summary* reviews clinical botulism, its epidemiology, and the therapeutic and potentially nefarious use of botulinum toxin.

CAUSATIVE AGENT

Botulism is caused by a potent neurotoxin produced by the anaerobic, Gram-positive bacillus *Clostridium botulinum*. There are seven antigenic toxin types, A–G; types A, B, E and occasionally F are associated with human disease.² The organism is found in soil throughout the world. Studies in the U.S. have shown that spores producing toxin type A predominate west of the Rockies, while type B spores are more predominant in the East. Type E spores are usually associated with the marine environment. Toxin type has significance for epidemiological and clinical reasons; illness caused by toxin type A is more severe and associated with a higher fatality rate.³ The toxin causes paralysis by binding (irreversibly) to receptors on nerve endings, entering the nerve, and interfering with the release of acetylcholine, causing flaccid paralysis.

* Supposedly it works for Cher.

CLINICAL FORMS

Botulism has three clinical forms. Foodborne botulism results from consuming preformed toxin in contaminated food. Symptoms usually begin within 12–36 hours of eating the dubiously prepared items. Home-prepared foods are more frequently implicated than those commercially prepared. Hardy spores can survive a less-than-meticulous canning process, because some strains require temperatures above boiling to guarantee elimination. Other factors important for inhibiting spores are low pH, high salt concentration and high redox potential (O_2). In an anaerobic, or near anaerobic environment, spores can germinate, reproduce and synthesize toxin. Foods that are spoiled, oiled, or foiled are great botulism incubators, and a variety of items have been implicated in foodborne botulism over the years. These include improperly canned or processed low-acid foods, including vegetables, meat, and fish; salted or fermented fish products; and whale or seal products. Outbreaks due to relish, chili peppers, salsa, foil-wrapped baked potatoes, garlic in oil, sautéed onions kept under butter sauce, and cheese sauce have been reported. The foodborne botulism case-fatality rate in the U.S. is currently 5–10%.

Intestinal botulism (formerly known as infant botulism) results from the colonization of the gastrointestinal tract with *C. botulinum*. The growing organisms produce toxin, which is absorbed *in vivo*. Intestinal botulism usually occurs in infants <6 months old.⁴ Ingestion of honey is a known risk factor, but the source is most often unknown. Constipation may be the first clinical sign. Infants present with lethargy, weak cry, decreased sucking, and weak bulbar and limb muscles. In very rare instances this intestinal colonization can occur in adults with gastrointestinal tract abnormalities resulting from diseases like Crohn's or from gastrointestinal bypass surgery.

Wound botulism occurs rarely and is the result of spore germination in an abscessed wound. Toxin is produced and absorbed at the site of infection. Before 1986, most described cases were the result of traumatic injury, but recently, cases are predominantly in illicit drug users—from either needle puncture sites in skin poppers or nasal lesions in chronic cocaine sniffers.⁵ Often the site of the botulinum toxin-producing abscess is not obvious. The incubation period can be several days. The case-fatality rate is around 15%.

SIGNS AND SYMPTOMS

No matter the mode of acquiring this neurotoxin, the clinical presentation is similar, although mild cases may be more difficult to recognize. The characteristic presentation includes dry mouth, sensation of a “thick tongue,” and blurred vision, along with cranial nerve impairment, marked by the “4 D’s” of diplopia, dysarthria, dysphonia and dysphagia. Symmetric, descending weakness and paralysis are typical. Severe cases require ventilatory support that may be needed for weeks or months.

DIAGNOSIS

Botulism is almost always diagnosed clinically, since commercial lab tests are not available to detect the picogram levels of toxin that cause illness. Muscle action potential augmentation with rapid (≥ 20 Hz) repetitive stimulation during electromyography is highly suggestive of botulism. Other conditions that must be included in the differential are Guillain-Barré syndrome, myasthenia gravis, stroke, tick paralysis, medication reactions, polio, and now, West Nile virus infection.

Laboratory testing using mouse bioassay (which involves waiting for mice to die, so it takes a few days) is available through the Oregon State Public Health Lab. If you really think your patient has botulism, treatment should not be delayed pending test



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results. Serum (5ml, get at least 2 red-top tubes) is used for toxin detection in cases of foodborne, wound and adult intestinal botulism. Stool (≥ 15 g) is tested for toxin in infant and adult intestinal, and foodborne botulism.

TREATMENT

Since the botulinum antitoxin works on unbound toxin only, it should be administered as soon as possible after first symptom onset in adult cases. The severity and duration of illness are reduced if the antitoxin is given early (although paralysis is not reversed).⁶ Antitoxin is accessible by calling the local health department any time day or night; the antitoxin will be shipped at no charge from the Sea-Tac quarantine station. The antitoxin used on adults is horse-derived. Infant botulism is treated with a human-derived hyperimmune globulin, which was recently approved by the FDA and is available through the California Department of Health Services for a mere \$45,300. Wound botulism treatment should include debridement and perhaps antibiotics, penicillin being the drug of choice.

BOTULISM IN OREGON

Since 1988, 51 cases of botulism have been reported in Oregon. Consistent with national epidemiology, the majority, 32 (63%) were infant intestinal, 13 (25%) were foodborne, 4 (8%) were wound, and 2 (4%) were adult intestinal. For those where toxin type was available, 85% were toxin type A, and 15% were B.

THERAPEUTIC USES

In the 1980s botulinum toxin became the first biological toxin licensed to treat human disease. Botulinum toxin in this

form, Botox,[®] is a dilute concentration of toxin A or B. It was originally licensed to treat cervical torticollis, strabismus and blepharospasm. It has also been used to treat various dystonias, migraine headaches, cerebral palsy, stroke, chronic low back pain and a variety of other conditions including hyperhidrosis. The effects of toxin injection can last several months to a year. Though systemic adverse effects are rare, generalized botulism-like syndrome after intramuscular injections of botulinum toxin type A has been reported.⁷

COSMETIC USES

Botox[®] was approved for cosmetic use in April, 2002. By paralyzing the underlying muscles, wrinkles are smoothed out—thereby clearing those pesky crows' feet and glabellar lines. The effect of a single treatment lasts 3 to 6 months. Botox[®] parties have been thrown in physicians' offices, spas, fitness centers and patient homes in some states in the U.S., but as far as we know, have not yet become popular in Oregon.

BIOTERRORIST WEAPON?

Botulinum toxin earned its status as a potential bioweapon because of its incredible potency (100,000 times more toxic than Sarin), ease of production and transport, and the severity of disease it causes. The toxin has a history as a bioweapon: the Japanese used it in Manchuria in the 1930s, and the U.S. and Soviets produced it in their biological weapons programs. Most recently, the Japanese Aum Shinrikyo cult dispersed it (ineffectively) on three separate occasions between 1990 and 1995. Should terrorists attempt to use botulinum toxin, it is postulated that the most likely mode of spread would be by aerosol dis-

semination (resulting in inhalational botulism) or contamination of food. On the positive side, the toxin is difficult to stabilize and concentrate for aerosol dissemination. Heating to an internal temp of 85° C for at least 5 minutes will destroy toxin (but not the spores!) in food or water. In the air the toxin is estimated to decay at 1% to 4% per minute.⁸ Factors that might indicate an intentional distribution include: many cases presenting at once; cases of an unusual toxin type (remember 85% of ours are A); patients with no common food exposures but with similar geography; and many simultaneous outbreaks with no common source.

THE BOTTOM LINE

A case of botulism, no matter how acquired, is big news,[†] and the health department can help (being the only source of CDC-released antitoxin). If you think you have a case of botulism, call.

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[†] Not to mention reportable by law.