

## Botox, the Poison that Heals

Ounce for ounce, a molecule made by the bacterium *Clostridium botulinum* is the most potent neurotoxin on earth. For millions of years, a tiny amount ingested or introduced to the body through wounds has been enough to paralyze all the muscles in a human or other mammal for months at a time, more than long enough to allow suffocation from respiratory failure. The structure and biology of this large molecule, primarily made of protein, was deciphered last century, but its ability to quickly and easily get into humans made it of great interest to both scientists and dictators around the world. After World War I showed that biological and chemical weapons could be mass-produced and used to kill entire battlefields of soldiers, interest in other deadly chemicals and biological molecules by all countries exploded, and botulinum toxin was quickly recognized as a potential deadly weapon.

So, leading up to World War II both the axis and the allies had a keen interest in understanding botulinum toxin and learning how to counteract its effects. In the United States, this effort primarily fell to the Army. Afraid that the Nazis would use it on the battlefields of Europe and elsewhere, a frantic rush was initiated to learn the properties of the toxin. Fortunately, few if any chemical weapons were ever used in World War II, and soon afterwards, interest in botulinum toxin and other agents waned.

Several scientists involved in these projects were physicians, and some of them came to understand that there could actually be medicinal qualities to this poison. One such interesting properties of botulinum toxin was its mechanism to weaken muscles by being taken up by the nerve endings attached to those muscles. This shuts down the nerve endings and their communication with muscles which keeps the muscles from contracting. When exposure is due to a bacterial infection, the toxin is widely distributed, coming into contact with nerves throughout the body, including those of the chest and diaphragm, resulting in breathing paralysis and eventual suffocation.

Some of the physicians wondered what would happen if a tiny amount of the toxin was isolated and injected right at a site of a muscle in doses that were too small to have any effect elsewhere. Using a small dose would preclude weakness developing throughout the body and produce effects just locally. In fact, this is exactly what happened; an ophthalmologist who was a previously involved with the Army project injected eye muscles of children with crossed eyes (strabismus), weakening the muscles that were pulling too far and straightening out the gaze. The results were very good with few or no side effects. Eventually, this piqued the interest of an eye care company which bought the patent and named the product Oculinum.

As any good capitalist knows, when you have a winning product, you find the broadest use for it. Because the primary effect of botulinum toxin was known to weaken muscles, the company, Allergan, looked for other disorders that might be improved by weakening muscles. Several neurologists at major universities recognized just such a disorder that could be helped. Cervical dystonia, also known as spasmodic torticollis, is an uncommon but disabling and painful disorder causing twisting and writhing of the neck muscles and pulling the head into all sorts of unnatural positions. In the mid-1980s, several studies began to show the benefit of injecting botulinum toxin into muscles of the neck, causing straightening of the head position and relief of pain. Recognizing that the current name was not indicative of its broader qualities, Allergan changed the name of the product to Botox, an obvious contraction of the name of the molecule itself. (At the same time throughout the rest of the world a nearly identical toxin, slightly different in its manufacture, was made and called "Dysport," and a slightly different molecule of the same family was created and given the name "Myobloc.")

Ultimately, many other indications came along, all based on the theory that relaxation of muscles can have a desired effect. For example, spasticity from a stroke or cerebral palsy can be ameliorated by injections into the affected muscles. Because the toxin also shuts down nerve endings that cause sweating, excessive armpit and hand perspiration can be reduced as well.

By far the most publicized application of Botox in particular has been for the treatment of wrinkles. For a decade now, the media has been awash with reports of the fountain of youth in a bottle. Although many misunderstandings about the mechanism and effects are prevalent, at its core Botox simply weakens the muscles of facial expression in areas where it is injected. Most of the time it is injected into the forehead and into the muscles around the eyes to reduce forehead lines and crow's feet respectively. An enormous success on its own, reports started coming in that patients with chronic headaches who received Botox for wrinkle treatment in the foreign were alleviated, incurring fewer headaches.

One variant of those headaches, chronic migraine, is one of the most disabling diseases on earth. In addition, few medications seem to help, and there had been no FDA approved treatment for this distressing condition. So a treatment that is given infrequently, about every three months, that doesn't require daily administration of a pill, that is not addicting, and that has few side effects, would be a game changer for millions of people. Such a thing has happened. Twenty years after Botox was brought into clinical use, studies have shown clearly that it can be useful in decreasing the severity and frequency of patients who have headaches at least half the days of a month.

In patients with 15 or more headache days a month, the reduction was approximately 8 to 10 fewer headache days per month. In addition, the headaches are generally less severe and more easily treated with other medications. Although a few patients don't respond at all, many have dramatic improvements, with very few headaches lasting up

to 2 1/2 or 3 months in between injections given about four times a year. Patients who were bed bound or would never go out in public or were taking large amounts of medications, including narcotics, now function nearly normally.

Neurologists all around the world are learning the technique, which is relatively simple, and finding the same responses everywhere. There is simply nothing better for the treatment of chronic migraine than Botox. The FDA recognized this and, two years ago in October 2010, approved Botox for the treatment of chronic migraine. Side effects are minimal and can include bruising, but except for occasional eyelid drooping from forehead injections or head heaviness from injections into the neck muscles, few patients have any significant problems. And because the effects wear off, all of these are temporary. Many skeptics, including this author, have become persuaded of its benefit, especially since patients continue to receive relief two years or more after starting treatment. Indeed, most placebo effects from new medications wear off after just a few treatments.

The mechanism of action regarding headaches is unknown. Some scientists suggest that the relief results from the interaction of Botox with sensory nerves as well as its known effect on motor nerves. There is evidence of this, but it remains a mystery how it works. Studies clearly show that it does not get into the brain or spinal cord and so does not affect pain centers there. The muscle relaxation itself probably doesn't play a huge role, though there are sensory receptors within muscle fibers that may be influenced.

The story of this poison that heals is truly fascinating and represents one of the most important medical advances in the last two decades. The future could be even more interesting, as it may be possible to use the properties of some parts of the botulinum toxin to bring other molecules into nerves and have effects on them. This may have implications in trying to restore function and vitality to weakened nerves from many diseases. But for now, millions of people have found that Botox is at least worth a shot.