Dystonia
Information Guide

INDIAN ACADEMY OF NEUROLOGY

A Public Information Initiative

What is dystonia?

It is a hyperkinectic movement disorder characterized by sustained or intermittent muscle contractions causing abnormal repetitive movements or postures. Dystonic movements are typically patterned and twisting which often worsen by voluntary action and are associated with overflow muscle activation.

What are the categories of dystonia?

Isolated dystonia is often referred to as primary dystonia, and when dystonia is associated with systemic disorder than it is secondary dystonia. There are many etiological factors which can cause isolated dystonia or secondary dystonia.

What are the different types of dystonia?

A. Focal/Segmental dystonias

- Blepharospasm (eyelid closure)
- Cervical dystonia (spasmodic torticollis)
- Laryngeal dystonia (spasmodic dysphonia)
- Limb dystonia (writer's cramp)
- Oromandibular dystonia
- Orolingual dystonia
- Truncal dystonia

B. Generalised dystonia

What are the treatment options for dystonia?

The current treatment of dystonia is symptomatic and based on three main strategies, according to the distribution and severity of the dystonia: medical treatment with oral medications, chemodenervation with botulinum toxin (BoNT), and surgical treatment with deep brain stimulation (DBS).

How do you decide the treatment of choice for dystonia?

Factors influencing the choice of treatment are age, severity, clinical presentation of dystonia, body distribution and co-occurrence of tremors. These factors should be considered before instituting any treatment.
Focal and segmental dystonia can usually be managed with BoNT, whereas oral medications are reserved for generalized form of the disease with or without additional BoNT.

Botulinum toxin - From poison to medicine

What is Botulinum toxin?

Botulinum toxin (BoNT) is produced by anaerobic gram-positive *Clostridium botulinum.* The clinical use of purified botulinum toxin (BoNT) represents one of the most dramatic role reversals in modern medicine: a potential evil transformed into a health benefit.
There are seven serotypes of BoNTs (termed A to G) only Onabotulinumtoxin are used A, Abobotulinumtoxin

A Incobotulinum A, and one BoNT-B serotype named Rimabotulinumtoxin B are commercially available for clinical use.

What is the mechanism of action of BoNT?

Clinical observations suggest that this neurotoxin have three mechanisms of action:

- Neuro-paralytic,
- Anti-secretary
- Analgesic (antinociceptive).

Effect at the neuromuscular junction and muscle spindle

Botulinum toxin acts by binding presynaptically to high-affinity recognition sites on the cholinergic nerve terminals and decreasing the release of acetylcholine, causing a neuromuscular blocking effect. This induces weakness of striated muscles by inhibiting transmission of alpha motor neurons at the neuromuscular junction.

What is the antinociceptive activity of BoNT?

It is postulated that BoNT A inhibits peripheral sensitization of nociceptive fibers, thereby, indirectly reducing central sensitization. BoNT A inhibits both substance P and Ach-mediated response in cholinergic neurons in animal studies. This proposed mechanism may be responsible for reduced pain perception and neurogenic inflammation.

How long does the effect of BoNT in dystonia lasts?

Improvement in dystonia starts about 1-7 days after the injection depending on the size of injected muscles. The effect peaks within two weeks to several weeks and then plateaus in milder forms before returning to baseline.

Clinically, this chemodenervation lasts between 12 to 16 weeks. Recovery from BoNT induced paralysis begins with re-sprouting of axon terminals and slow recovery of the ability of neurons to release acetylcholine, resulting in nerve conduction getting reestablished.

What are the adverse events associated with BoNT?

These are mild and temporary, and may be dose- or site-related. These may include local reactions, such as bruising and pain at the site of injection, and sometimes excessive localized muscle weakness may also be noticed due to spread of toxin to other muscles.

Systemic effects are very rare and may include flu-like symptoms, light-headedness and dry mouth. These are far less common, are generally short-lived, and may result from the systemic spread of the toxin. However, until today, no causal relationship confirmed the evidence relating this specific adverse event to the BoNT.

What are the factors responsible for formation of antibodies?

Since all BoNT are proteins, so with repeated injections, immunoresistance may develop secondary to antibody formation. The incidence of antibody-mediated resistance in long-term treated patients ranges from 3 to 25%. The common factors responsible for antibody formation are:

- Product-related factors such as manufacturing and storage processes, further, antigenic protein load and presence of non-toxic accessory proteins (NAPs) of each formulation can influence the immunogenicity.
- The other reason is the dose used per injection. Development of neutralizing antibodies is correlated to the increasingly cumulative doses of BoNT used.
- Frequency of injections. If the injection interval is shorter than 2 months it may increase the risk for formation of neutralizing antibodies.
- Finally, previous exposure or vaccination against BoNT may also affect immunogenicity.

There is a new BoNT-A developed which is free of NAPs, hence, low rate of neutralizing antibodies formation and improved immunogenicity profile.

Therapeutic uses of BoNT in dystonia

Blepharospasm

BoNT was first approved by FDA in 1989 for the treatment of blepharospasm, making it the first botulinum toxin type A to be commercially useful.

BoNT is injected into both eyebrows and the orbicularis oculi muscle. The average dose of BoNT/A is 10 U in each eyebrow, 10 U in the upper eyelid and 5 U in the lower eyelid. BoNT into the pretarsal rather than the preseptal portion of the orbicularis oculi is more effective and is associated with lower frequency of ptosis (drooping of eyelids). Moderate to marked improvement is usually noted in over 90% of patients treated for blepharospasm.

Oromandibular Dystonia

It is among the most challenging forms of focal dystonia to treat as it rarely improves with medications. The masseter muscles are injected in patients with jaw-closure dystonia (average dose = 30 U per muscle), and the lateral pterygoid and/or submental muscle complex is injected in patients with jaw-opening dystonia (average dose = 20 U). A meaningful improvement in chewing and speech is achieved in more than 70% of all patients.

Laryngeal Dystonia (Spasmodic Dysphonia)

In the treatment of laryngeal dystonia, BoNT is now considered as the treatment of choice. In adductor dystonia, the toxin is injected through a monopolar, hollow, teflon-coated needle directed into the thyroarytenoid muscle. The dosage can be adjusted depending on the severity of glottal spasms and the response to previous injections.

Cervical Dystonia

BoNT causes improvement in 90% of patients with cervical dystonia. Proper dose and site of injection have been shown to be the most important determinants of a favorable response to treatment. The average latency between injection and the onset of improvement is about 1 week, and the average duration of maximum improvement is 3 to 4 months. On average, the injections are repeated every 4 to 6 months. Less than 5% of patients fail to improve after repeated injections.

Writer's Cramp and Other Limb Dystonias

BoNT injections into selected hand and forearm muscles provide the most effective relief in patients with these task-specific occupational dystonias. Temporary hand weakness may be noticed in 30% of patients.

Local injection of BoNT may benefit patients with foot dystonia as a manifestation of idiopathic torsion dystonia, or patients with parkinson's disease.

Hemifacial Spasm

Hemifacial spasm is not only annoying, but also socially embarrassing. BoNT injection in the involved facial muscles causes improvement in nearly all patients. The approach can be individualized by injecting only in those muscles whose contractions are most disturbing to the patient. The average duration of improvement of hemifacial spasm is about five months, which is longer than the dystonic disorders.

Conclusion

The safety, effectiveness, specificity, and reversibility of BoNT make it a powerful and versatile tool in a wide variety of neurological disorders. It is likely that the applications of BoNT therapy will continue to expand in the future.

It is of note that, less than 5% of those treated for cervical dystonia and rare patients treated for other disorders have become resistant through development of blocking antibodies . Some of these patients have benefited from injections by different preparations of BoNT type A86 or BoNT types B and F.

Disclaimer:
This brochure is for the general information of the public and the patients. People should not self-medicate themselves with the medicines and treatments mentioned here. Before taking any of the medications mentioned in the information brochure, please consult your neurologist.

Dr. B. S. Paul, *MD, DM*

INDIAN ACADEMY OF NEUROLOGY