Botulinum Toxin Therapy for Dystonia: Reasons for Treatment Failure

Figure 1

Figure 1 Original illustration by “Phiz” (Hablot Knight Browne) of Jeremiah Flintwinch (centre) and his “twisted” neck.

“His head was awry, and he had a one-sided, crab-like way with him, as if his foundations had yielded at about the same time as those of the house, and he ought to have been propped up in a similar manner”; “His neck was so twisted that the knotted ends of his white cravat usually dangled under one ear...he had the weird appearance of having hanged himself at one time or other”
Introduction

Nineteenth-century Victorian novelists Charles Dickens provided several detailed accounts of movement disorders in his literary works, many of which predated medical descriptions. The above quote provides a possible description of cervical dystonia, a form of focal dystonia arising from involuntary activation of muscles in the neck and shoulders causing turning, tilting, flexion or extension movements of the head.

Dystonia is a disorder of movement defined as a syndrome of sustained contractions causing twisting or repetitive movements or abnormal postures. It may be classified in a number of different ways. One classification of dystonia depends on the distribution which may be generalised, segmental where it affects contiguous body parts, or focal when affecting only a single body part (Table 1). Although cervical dystonia, most often producing torticollis, is perhaps the best known example of focal dystonia, other focal dystonias include blepharospasm, resulting in repetitive forceful eyelid closure; spasmodic dysphonia affecting speech; tongue, jaw opening and jaw closing referred to as oromandibular dystonia.

<table>
<thead>
<tr>
<th>Focal Dystonia: Single body part affected:</th>
<th>Dystonia</th>
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<tbody>
<tr>
<td>Eyelids</td>
<td>Blepharospasm</td>
</tr>
<tr>
<td>Mouth</td>
<td>Oromandibular dystonia, musician cramp</td>
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<tr>
<td>Larynx</td>
<td>Dystonic adductor dysphonia or whispering dysphonia</td>
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<tr>
<td>Neck</td>
<td>Cervical dystonia, previously known as spasmodic torticollis</td>
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<tr>
<td>Hand and Arm</td>
<td>Writers cramp</td>
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</tbody>
</table>

Segmental dystonia
<table>
<thead>
<tr>
<th>Segment</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cranial</td>
<td>Two or more parts of the cranial and neck musculature</td>
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<tr>
<td>Axial</td>
<td>Neck and trunk affected</td>
</tr>
<tr>
<td>Brachial</td>
<td>One arm and axial; both arms with or without neck, with or without trunk</td>
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<tr>
<td>Crural</td>
<td>One leg and trunk; both legs with or without trunk</td>
</tr>
<tr>
<td>Generalised Dystonia</td>
<td>Combination of segmental crural and any other segment</td>
</tr>
<tr>
<td>Multifocal Dystonia</td>
<td>Two or more non-contiguous parts affected</td>
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<td>Hemidystonia</td>
<td>Ipsilateral arm and leg</td>
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</table>

Although this classification is widely used, the definitions do not always represent the salient clinical features, and some additional points deserve to be noted. Focal dystonia may also be task-specific for example; writer’s cramp, which was first recognised as “scrivener’s palsy” in 1855 and was defined in the Encyclopaedia Britannica 1877, as dystonia affecting the hand or arm during the act of writing. This task specificity may also be seen in other forms of dystonia, such as musicians’ dystonia. Abnormal muscle contractions, sometimes involving the co-contraction of agonists and antagonists, often produce highly stereotyped movements in individual patients.

Another way of classifying dystonia is according to aetiology; Primary torsion dystonia (also known as ‘idiopathic torsion dystonia’) is that in which dystonia the sole symptom is. Most patients with primary dystonia do not have a family history, but families with multiple affected individuals are well described. The term ‘dystonia-plus’ refers to conditions in which dystonia is one of only two main neurological features present, the other usually being myoclonus or parkinsonism. Heredodegenerative dystonias are those in which the dystonia is part of a more widespread neurodegenerative syndrome, often with a known inheritance pattern.
Secondary (‘symptomatic’) dystonias are caused by environmental insults such as strokes, tumours, infections, drugs and toxins. Except for tardive dystonias (for which no predisposing genes have been identified), the secondary group do not obviously have genetic causes and will not be considered further here. The classification by aetiology is particularly useful, because the presence of neurological features other than dystonia immediately suggests that dystonia-plus, a heredodegenerative syndrome or a secondary dystonia is present. However, it should be noted that the converse is not always true, since some secondary dystonias can present with pure dystonia.

As well as aetiology and distribution dystonia classification can sometime be thought according to age of onset. When symptoms begin before the age of 26 years, they are termed early-onset dystonia. If the symptoms begin after this age, they are classified as late-onset dystonia. In most cases early-onset dystonia tends to generalise whereas late-onset dystonia remains focal (figure 2). Therefore this classification is useful as it can provide prognostic factors for clinical progression.

(Figure 2) The data based on patients seen at the Neurological Institute, Columbia Presbyterian Medical Centre, Columbia University, New York, USA.
What is fascinating and unifying about this heterogeneous disorder is that it is thought the neural mechanism underlying all dystonias involve a common final pathway of reduced inhibition of thalamocortical output resulting in simultaneous contraction of agonist and antagonists muscles.  

**Rationale**

The prevalence estimates for primary dystonia range from two to 50 cases per million for early-onset dystonia and from 30 to 7320 cases per million for late-onset dystonia. Cervical dystonia is the most common form of focal dystonia with an estimated prevalence rate in Europe of 5,7/100000. Dystonia can affect patients of all ages and can impact patient’s quality of life considerably. Hallett and colleagues reported pain in approximately 60% of patients with cervical dystonia, and this can be the most disabling feature. Embarrassment with social withdrawal is another important incapacitating feature.

Dystonia is a chronic condition with no curative therapy only treatment is to ameliorate symptoms. Botulinum toxin (Bt) injections are often the first line of treatment for focal and segmental dystonias administered by injection to the affected muscles; doses are tailored according to the severity of symptoms / signs, size of the muscle and the individual patient. Symptomatic relief peaks about 2-weeks after treatment and may last for 3-4 months as new motor nerve axon terminals start sprouting soon after the Bt injection. However there is a reported failure rate of treatment; one study looking at spasmodic dysphonia (laryngeal dystonia) showed Bt therapy was ineffective at least once in 80% patients during follow-up. Furthermore, in treatment of cervical dystonia abnormal head and neck
posture is not completely relieved in some patients, despite symptomatic improvement\textsuperscript{12}

The aim of this essay is to review the reasons why Bt fails in the treatment of dystonia. I will begin by looking at background of Bt as a therapy in dystonia, then I will attempt to evaluate the potential reasons why treatments may fail.

\textbf{Botulinum Toxin}

Botulinum toxin is a natural product synthesised by a gram negative anaerobic bacterium \textit{Clostridium botulinum}. It is responsible for the food poisoning disease botulism. The history of the discovery of Bt to its clinical application as a therapy is both intriguing and instructive.

The German poet and district medical officer Justinus Kerner (1786-1862) published the first descriptions of the symptoms of food-borne botulism, which he termed “sausage poisoning” and this led to the term botulism (botulus being the Latin term for sausage). Reports from the end of the 18th century during the Napoleonic wars described some well-documented outbreaks of “sausage poisoning” in Southern Germany. These patients were likely to have been affected with food-borne botulism having signs of dilated pupils and fatal muscle paralysis. Kerner was also the first to develop the idea of a possible therapeutic use of the toxin; he concluded that the toxin applied in minimal doses, should reduce or block the hyperactivity and hyper-excitability of the motor and the autonomic nervous system.\textsuperscript{12}
**Use in Dystonia**

Bt was not introduced as a therapy for dystonia until the late 1980s, it since has revolutionised treatment by offering a targeted approach to symptom relief for many sufferers.

Different strains of Clostridium botulinum produce seven immunologically distinct forms of botulinum neurotoxin that are labelled BtA through to BtG. Studies by Brin and colleagues showed that these potent neurotoxins are metalloproteases that block the release of acetylcholine at the neuromuscular junction though the cleavage of different peptide bonds that are crucial components in synaptic vesicle to membrane fusion. Not all nerve terminals will be affected by the toxin, allowing the injected dystonic muscle still to contract, but with less force. This weakness allows for improved function of the dystonic muscle(s) and therefore posture. The degree of weakness depends on the dose, and the duration of effect is further dependent on the serotype employed. Types A and B have been shown to be safe and effective in double-blind clinical trials for the treatment of dystonia. One formulation of BtA is marketed worldwide under the name BOTOX® (Allergan Inc.) and another in Europe as “Dysport” (Ipsen, UK). “BOTOX®” was approved in 1989 by the US Food and Drug Administration (FDA). A formulation of BtB was approved in 2000 by the FDA for treatment of cervical dystonia, marketed under the name “Myobloc” in the US and “Neurobloc” in Europe.
Reasons for treatment failure

The success of a botulinum toxin injection depends upon certain factors.

(1) Dose

Biological activity varies within different commercial formulations; therefore the administration of Bt therapy for the focal dystonias requires an understanding of the toxin itself, preparation of various dilutions, and practical knowledge of typical dosages. One issue lies with the apparent different potencies of BtA (Dysport and Botox). There are only two randomised controlled studies which have tried to determine the conversion factor representing bioequivalence\(^{30,31}\). It is therefore potentially hazardous to use both drugs in the same clinic at the same time as mistakes can be made.

Many factors affect the dose of Bt including severity and chronicity of the disease, number of muscles involved, previous response, concurrent medical therapies, and the experience of the person performing the injection. The optimal dose of Bt is a balance between the lowest dose of Bt required to achieve the desired outcome (e.g., decreased muscle tone, reduction of muscle spasms, improved range of motion and function) without adverse effects i.e. weakness of the muscle which interferes with function.\(^{16}\) Patients who do not respond to the first injection of Bt are referred to as "primary non-responders," but reasons for non-response can include inadequate dose.\(^{28}\) Therefore a patient should not be considered a primary non-responder until incremental dose increases or clinical tests have been tried. A study by Hanna & Jankovic suggests the most useful test to confirm poor response – i.e. biological failure – is to inject Dysport (20 mouse units) or Botox (7.5
mouse units) into the frontal muscle above one eyebrow. A positive response should be revealed by asymmetry of the forehead on attempted frowning.\textsuperscript{14}

2) The specific injection site

Optimal results are obtained when treatment strategy is based on careful neurological evaluation, and only the involved muscles are injected with an appropriate dose. If Bt is not injected into the appropriate muscles, treatment is likely to be ineffective. Deep muscles may be involved but can be difficult to palpate and inadequate localisation of target muscles is a major cause of treatment failure\textsuperscript{17,18}

Needle EMG can detect the abnormal firing of the motor unit action potentials of dystonic muscles \textsuperscript{19,20}. Therefore mapping based on this technique is the most widely used method for reliably identifying dystonic muscles. However, not every neck muscle can be explored with a needle electrode. For example, deep cervical muscles may be beyond reach with a conventional 37-mm needle electrode \textsuperscript{21}.

In addition, accurate placement of the needle electrode tip into a muscle is often difficult in patients with a severe dystonic posture. Moreover, knowledge of anatomy that is sufficient for routine EMG is not always sufficient for injections. For example, if the problem affects only the middle finger, it is not enough to find the flexor digitorum superficialis; the injection should be into the fascicle of that muscle specific for the third finger.\textsuperscript{23}

A study by Sung and colleagues suggests the use fluorine-18 fluorodeoxyglucose [(18)F]FDG and positron emission tomography (PET) to localise dystonic muscles. As glucose metabolism and 18F-FDG uptake are enhanced in contracting
skeletal muscles\textsuperscript{24}, the authors hypothesised that the degree of 18F-FDG uptake may be associated with the strength of contraction of skeletal muscles. This study found 18F-FDG PET/CT was useful for localising dystonic cervical muscles in all six participants with idiopathic cervical dystonia.\textsuperscript{25}

Even after identifying the correct muscles the majority of the toxin is deposited into the mid-belly of the muscle. The toxin BtA has its effect only at the endplate, and in quantitative studies it has been demonstrated that the toxin is more effective if delivered at the endplate. It would be useful, therefore, in principle to identify and inject into the endplate zone, but given the large size of the endplate zone and the diffusion of the toxin, the recommendations made, is that injection is made into the mid-belly of the muscle.\textsuperscript{26}

To be effective as a treatment for adductor spasmodic dysphonia, Bt must be injected into the vocal folds and precisely into the thyroarytenoid muscle\textsuperscript{22}, where it must induce chemodenervation. Some studies have reported mislocation of injection site and varying injection efficacy which may be due to individual anatomical differences of these muscles or possible concurrent dystonia of extraphonatory muscles.\textsuperscript{10} In addition, vocal folds are obviously under adduction, so they should be traced by inserting the needle in the cricothyroid space at the mid-line, thus being almost parallel to the sagittal axis; during injection, however, patients are naturally often tense, keeping under forced inbreathing, with their vocal folds abducted, requiring the needle to be tilted to form a 15°–30° angle with the sagittal plane (figure 3).
(3) The experience of the clinician

The reason for variable effects from one injection to another in the same patient are still somewhat uncertain, although this may depend on technical aspects of the injection procedure. As mentioned previously the experience of the clinician is one of the factors, as is the dose employed, in addition to clinically correctly identifying the dystonic muscle to ensure the correct muscles are being injected. Cervical dystonia is common but no two cases are identical and the muscles to inject and the dosages used are left to the clinician’s discretion. Therefore before injecting it is important to spend time observing the patient’s neck movements and asking the patient which muscles are likely to be the overactive muscles.

To improve outcome the clinician administering Bt must have a good understanding of both the anatomy of affected muscles and the nature of the resulting movement disorder. Prior to treatment with Bt, patients should undergo full neurologic evaluation and examination. Secondary causes of dystonia such as drugs or conditions such as Wilson disease must be ruled out before commencing treatment with Bt.

(4) Communication between Doctor and patient
The patient must be advised that the treatment is not a cure and not everybody will gain benefit and injections will have to be repeated to sustain relief. It is essential the doctor takes time to elicit the patient’s main problem and disability and both parties agree on symptoms and what should be expected as some patients’ expectations may be unrealistic. Patients may report failure of treatment even after having striking improvement having anticipated complete recovery. Patients with associated disorders, particularly alcoholism or depression, often report poor response despite clinical evidence of motor weakness. Doctors must be cognisant of this and often useful to follow up patients and assess improvement by use of analogue scales example, for example the Dystonia Rating Scale/UDRS. Photographs or video recordings of the patient taken with consent and stored securely before treatment commences are often helpful in reassuring patients about their progress and improvement, particular as the degree of incremental improvement while often dramatic initially, may decrease with successive injections and the overall improvement may plateau. It can then be helpful to remind patients of their initial clinical symptoms by this means. If Bt is not adequate, medications should be considered as adjunctive therapy.

(5) Development of antibodies
Botulinum neurotoxins may be immunogenic and it is clear that up to 5% of patients develop secondary failure as a result of the development of antibodies which bind to and inactivate Bt causing biological resistance. The only sign of the development of antibodies is lack of response to further injections. The use of other serotypes (F or B) may benefit those who have developed antibody resistance. Risk factors for the development of antibodies include higher doses,
shorter intervals between injections, booster doses, and young age. Recommendations have been made to help prevent development of antibodies; these include: using the smallest possible dose to achieve relief, a minimum of nine weeks interval between injections and avoidance of "booster injection." It is also good clinical practice to postpone re-injection until the dystonic signs have recurred\textsuperscript{29}, and this will allow reassessment of the patient.

The immunogenicity is a concern as dystonias are a chronic condition requiring long term therapy. In 2008 Xeomin was launched in the UK as the third BtA free of the complexing proteins which are thought to play a role in the formation of antibodies. Xeomin has not been associated with any biological immunogenicity in animal models and is likely to be associated with fewer neutralising antibodies\textsuperscript{36}. The Scottish Medicine Consortium has approved the use of Xeomin within NHS Scotland for management of blepharospam and cervical dystonia.\textsuperscript{37}

\textit{Conclusion}

Despite an incomplete understanding of the neurological mechanisms underlying dystonia, relief of dystonic posturing and associated pain and discomfort has improved markedly since the introduction of botulinum toxin therapy in the late 1980s, so much so, that it has become the standard therapy for focal dystonias. However Bt does not always provide satisfactory results which can be a challenge for both the patient and the treating doctor. Priorities for future research in this area include randomised controlled trials of BtA preparations which lack complexing proteins, such as Xeomin, to determine whether these are less immunogenic than conventional BtA. Alternative superior neuromuscular junction–blocking agent with a prolonged duration of action is another
possibility. These developments might help to prolonging the therapeutic effect and possibly provide benefit for those patients were treatment fails due to neutralising antibodies. However treatment failure often is multi-factorial and other explanations are more likely and may be more easily resolved by careful evaluation of the patient and rigorous targeting of affected muscles.

This essay has outlined the main causes of failure of treatment with Bt. Rigorous clinical examination of the patient to identify correct muscle groups, careful attention to injection site and technique employing EMG guidance where necessary, effective communication with the patient to elicit the impact of dystonia on function and activities of daily living, and agreeing the goals of treatment, will all help to improve individual outcomes and minimise adverse events.
References


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