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USE OF BOTULINUM TOXIN IN TARDIVE DYSKINESIA AND TARDIVE DYSTONIA: TRANSFORMING PATIENTS INTO SWANS?

Botulinum toxin is frequently recognized as having cosmetic applications in treating glabellar lines, horizontal forehead lines, crow's feet, and brow sag. Investigational uses of botulinum toxin include headache (including migraine), tremors, urinary incontinence, lower back pain, and tic disorders. It appears that botulinum toxin may also have a role in the treatment of tardive dyskinesia and dystonia. This newsletter will attempt to review the role of botulinum toxin in tardive dyskinesia and dystonia.

Tardive dyskinesia and dystonia

Tardive dyskinesia is an involuntary movement disorder that may result from long term neuroleptic exposure. It is characterized by stereotypical and repetitive movements of the orofacial areas (tongue, lips, face), trunk, and extremities. These movements can vary in intensity over time, increase with emotional arousal, decrease with relaxation and disappear during sleep. The pathophysiology of tardive dyskinesia is not completely understood; however, there are a few proposals that have been suggested to help explain the development of tardive dyskinesia. The dopamine supersensitivity hypothesis suggests that chronic administration of dopamine antagonists results in the increase in the number or sensitivity of dopamine receptors to dopamine and thus leading to the hyperkinetic state. The gamma-aminobutyric acid insufficiency

hypothesis suggests that chronic neuroleptic treatment results in a decrease in GABA function and an increase in GABA receptors. The neurodegeneration hypothesis states that tardive dyskinesia is a result of neuronal cell damage due to the production of free radicals and increased oxidative stress. Finally, the synthetic view acknowledges each hypothesis as there is evidence to support each one. Risk factors for the development of tardive dyskinesia include advancing age, females, smoking, alcohol & drug abuse, diabetes mellitus, presence of negative symptoms of schizophrenia, affective illness and long term treatment with neuroleptics. Criteria for the diagnosis of tardive dyskinesia include the presence of choreiform (rapid, jerky, nonrepetitive), athetoid (slow, sinuous, continual), or rhythmic (stereotypes) involuntary movements for at least 4 weeks, developing during exposure to at least 3 months of neuroleptic usage (1 month if >60 years old) or within 4 weeks of withdrawal of oral neuroleptics (or 8 weeks if depot).

Tardive dystonia is a specific type of movement disorder that is characterized by a muscle spasm leading to abnormal posturing and may also occur after months or years of neuroleptic exposure. Frequent areas of involvement include the neck (retrocollis-head and neck pulled back between the shoulder blades, torticollis-head and neck turned to the side), eyelids (blepharospasm), tongue, jaw, face, trunk, or limbs.

Traditional treatments of tardive dyskinesia and dystonia other than avoiding the causative agent

include benzodiazepines (clonazepam), muscle relaxants (baclofen), dopamine depleting drugs (reserpine, tetrabenazine), vitamin E, or a switch to clozapine. Although the use of botulinum toxin (BTX) has been frequently reported for the treatment of strabismus, focal dystonias (blepharospasmodic, cervical, oromandibular, spasmodic), tremors and hemifacial spasm, there is limited data regarding its use specifically for tardive syndromes and its safety and efficacy in conjunction with neuroleptics.

Botulinum toxin: Review of the Literature

Botulinum toxin is derived from the anaerobic bacterium, *Clostridium botulinum*. At the neuromuscular junction, it appears to bind to the presynaptic nerve terminals and block acetylcholine release from the nerve endings. The result is the blocking of neurotransmission and a focal muscle paralysis. There are many subtypes of botulinum toxin, including types A to G and each subtype evokes distinct immunological responses. The clinical use of type A, B, and F are more frequently described in the literature and it appears that both type B and F have a shorter duration of action compared to type A. So far, only type A has currently been reported for the treatment of tardive dyskinesia and tardive dystonias.

Truong, D.D. (1990) reported 3 cases of the use of botulinum toxin in tardive dystonia and dyskinesia. The first case was a 60 year old woman who developed orofacial movements, repetitive blinking, involuntary mouth closure, and retrocollis after taking haloperidol for 1 month. For the involuntary jaw closure, she was given 40 U into each masseter muscle. For the retrocollis, she was given 40 U to the splenius capitis muscles and 35 U into each semispinalis capitis. After 2 weeks, she could open her jaw easily and the retrocollis had disappeared; this effect lasted for 2 months. The second case was a 50 year old woman who developed repetitive

movements of the mouth, choreatic tongue movements and continual bruxism (rhythmic or spasmodic gnashing, grinding, and clenching of teeth) after taking haloperidol for 10 years. She was given 25 U into each masseter muscle and 12.5 IU to each temporalis muscle. By the second day, her grinding disappeared and by the second week, significant improvement in bruxism was noted. New choreatic side-to-side movements of the jaw appeared possibly previously masked by the forceful closure of the mouth. As a result, a second BTX treatment (12.5 U) was given to the pterygoid muscle and to each masseter muscle and this resolved grinding, choreatic side to side movements, and bruxism after 2 weeks. A third case was a 76 year old woman who developed repetitive blinking, movements of the mouth (including tongue), neck, feet, twisting of the arms, and rocking of the body after being treated with haloperidol for 6 months when she was 66 years old. She was given BTX to the right sternocleidomastoid muscle, right trapezius, and left splenius capitis muscle. Significant improvement in head movements was seen 3 weeks later and this lasted for 3 months. Body rocking and mouth movements were further reduced with the addition of reserpine.

Stip, E. et al (1992) used BTX-A in a 41 year old man with a 23 year history of neuroleptic use (chlorpromazine, trifluoperazine, haloperidol, thioridazine, methotrimethazine, haloperidol, fluphenazine). He developed mixed dyskinetic and dystonic movements of the face, jaw, and neck, and abnormal movements in the shoulders. He was given 3 injections of 75 U each to the left splenius capitis and right and left trapezius. The treatment relieved these abnormal movements and injections continued to be given every 4 months. During the first 10 days after injection, he experienced flexed position of the neck and intermittent dysphagia.

Kaufman, D.M. (1994) reported efficacy with the use of BTX-A in 3 separate cases of tardive torticollis that developed after prolonged

treatment with neuroleptics. The first case was a 41 year old woman who was treated with combinations of haloperidol, perphenazine, lithium, and benztropine over at least 3 years. She developed continual involuntary and spasmodic movements of the neck and head and was treated with 12 equal injections of BTX-A totaling 150 U. She experienced pain relief and improvement in movement 10 days after the first injection and this lasted for 3 months. The second case was a 42 year old man treated with fluphenazine decanoate and other unknown antipsychotics for an unknown duration. He experienced a continual tilting of his head to the right and his head and neck rotated to the left. He was given a number of BTX-A injections, totaling 200 U. He experienced an improvement in cervical pain that lasted for about 2 months and a reduction in movements to intermittent spasms. The third case was a 43 year old woman who was treated with haloperidol and lithium for an unknown duration. She developed retrocollis of the neck, characterized by the extension of her head and neck, and the bulging of her neck muscles in spasmodic contractions. Six equal injections of BTX-A totaling 75 U were given and an improvement in movements and pain was evident after 1 month. One month later she was given another set of injections and she reported a resolution of her movements and pain 2 weeks later. In each of these cases, there were no reports of any systemic side effect or complications of neck weakness.

Yusufuku-Takano, J (1995) reported a unique case of tardive dyskinesia in a 43 year old woman presenting with severe involuntary movements as a result of treatment with haloperidol, fluphenazine, and biperiden for approximately 15 months. Her symptoms consisted of tongue twisting, intermittent and tonic retroflexion of the neck and trunk, and repetitive extension and flexion of the limbs. As a result, she was confined to bed, unable to walk, stand or sit, and could not feed herself. She was given 3 pairs of BTX-A injections (each 50 U) to the posterior cervical region. The peak effects were evident 7-10 days

after the 1st injection as the retroflexion of the neck became less frequent and severe. She was more stable while sitting and started to feed herself. A second injection was given 2 weeks after the first and a third injection 6 week later. Retroflexion of the neck continued to improve, involuntary movements of the limbs improved, and her posture became more stable so that she could walk. These improvements were maintained for >20 months with continued BTX injections given at intervals of 3-6 months. The injections were well tolerated as she did not report any weakness in her limbs after the treatment.

Chatterjee et al (1997) performed a retrospective case series on 22 patients treated with BTX-A alone or with psychotropics and muscle relaxants. An IM injection of varying doses was given to the neck (mean dose 161.2 U x 3.1 injections), eyes (mean dose 4 U x 4 injections), vocal cords (mean dose 2.5 U x 2 injections), jaw (mean dose 78.5 U x 3 injections), and face (mean dose 58 U x 2.7 injections). The side effects experienced were usually site dependent, mild, and transient. Ptosis (drooping of upper eyelid) occurred in 2 patients who were treated for blepharospasm, dysphagia occurred in 2 patients who were injected in the neck and the vocal cords, and flu-like symptoms occurred 4 days after treatment developed in 1 patient. There were 3 remissions but it is unclear if it was directly related to the use of BTX. Aside from the remissions, the authors reported a clinically significant benefit of the injections that lasted for several months.

Tan, E.K. and Jankovic, J. (2000) performed a retrospective study on 24 patients with tardive oromandibular dystonia, with jaw opening and mixed dystonias being the most frequent occurrence. The mean duration of neuroleptic use was 7.1 years. BTX-A was given to the masseter (mean dose 56.3 U) and submental muscles (mean dose 29.4 U). The authors reported duration of benefit from the injection lasted about 16 weeks.

Role of botulinum toxin in tardive dyskinesia and dystonia

Based on retrospective studies and case reports, botulinum toxin has a potential role as an alternative treatment for tardive dyskinesia and dystonia. These reports describe rapid symptom relief and improvement in quality of life from small doses of botulinum toxin A. The effects can be seen almost immediately at the site of injection and the peak onset of improvement as early as 1 week. In terms of duration, the effects can persist up to 3-4 months after the last injection. The side effects of botulinum toxin usually correlate with the site of injection. For instance, ptosis has been described in patients treated for blepharospasm, dysphagia in patients treated for torticollis, and general weakness of the injected muscles. The development of antibodies against the toxin has also been reported when botulinum toxin has been used repeatedly over a long period of time or when large doses were used. The significance of this finding is reduced or absent clinical response after repeated injections. Therefore, to avoid sensitization, it is recommended that doses do not exceed 100 units per injection cycle. There are currently no contraindications to the use of botulinum toxin; however, its teratogenicity has not yet been established.

There have been few reports describing the use of botulinum toxin in tardive dyskinesia compared to dystonia possibly because dyskinesia is more complex and often involves different muscle groups. If botulinum toxin is to be used in tardive dyskinesia, it is important to identify the most involved muscle groups for injection in order to achieve the most benefit with the least amount of toxin. As tardive dystonias frequently involve distinct muscle groups, injections directly given to these areas should provide rapid relief from pain and spasms.

There are no clear guidelines in terms of dosing for tardive dystonia and dyskinesia. Here is a

summary of the range of doses for BTX-A used based on the available literature:

Tardive dyskinesia:

3 pairs of 50 U each for treatment of repetitive retroflexion of the neck may help resolve involuntary movements of the limbs (Yusufuku-Takano, J).

Tardive dystonia:

Site/Type	Dose used
Neck	160 U x 3 injections ^c
Retrocollis	35-40 U ^t
Torticollis	A series of 12.5 U injections totaling 75-200 U ^k
Eyes	4 U x 4 injections ^c
Vocal cords	2.5 U x 2 injections ^c
Jaw	78 U x 3 injections ^c
Choreatic side-side movements of the jaw	12.5 U ^t
Involuntary jaw closure	40 U ^t
Bruxism	12.5-25 U ^t
Oromandibular	29-56 U ^{tj}
Face	58 U x 3 injections ^c

^c Chatterjee et al.

^t Truong, D.D.

^k Kaufman, D.M.

^{tj} Tan, E..K and Jankovic, J.

Conclusion

In order to clarify the therapeutic role of botulinum toxin in tardive syndromes, well-designed, prospective, randomized, double-blinded clinical trials should be performed. Studies comparing varying doses may help further optimize the dose for each type of abnormal movement, balancing both efficacy and undesired effects. It currently may be considered a treatment for tardive dyskinesia and tardive

dystonia when the movements are debilitating or life threatening and have been unresponsive to other pharmacological interventions. It is also necessary to establish safety of long term treatment with botulinum toxin A and to establish role of other botulinum subtypes for those who are resistant to subtype A.

Botulinum toxin type A is currently marketed in Canada by Allergan under the trade name Botox®

at a cost of \$340.00 per vial. Each vial contains 100 units of botulinum toxin and is supplied as a powder to be reconstituted prior to injection. The powdered form must be stored in the refrigerator (2-8 °C) and once it is reconstituted, it is stable for 4 hours.

Please email jkim@bcmhs.bc.ca for any comments, questions or concerns with the content of the newsletter.

“For Your Inpharmation” is published quarterly and it is available on the Riverview Hospital website at http://www.bcmhs.bc.ca/library/content_handler.asp?content_file=Inpharmation/Inpharmation.asp

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