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Systemic Weakness After Therapeutic Injections of Botulinum Toxin A: A Case Series and Review of the Literature

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Abstract

The use of intramuscular injections of Botulinum neurotoxin A (BoNT-A) is common in the treatment of hypertonicity and movement disorders. While most side effects are mild, systemic effects, manifested by generalized weakness distant from the site of injection, have been reported. Previously reported occurrences are discussed, and three new cases of patients who developed systemic weakness following administration of BoNT-A (Botox®), despite having tolerated similar injections on several prior occasions, are presented. A review of the literature and reported cases indicate that risk of developing systemic effects does not appear to be related to dose based on body weight. It may be more likely that risk for systemic effects is related to total injection dose and injection frequency. The results of our three patients would indicate that injections of greater than 600 units of Botox with follow-up injections occurring every three months may lead to an increased risk. We would recommend careful consideration of re-injection frequency if injections of greater than 600 units of Botox are given. Reduction in systemic side effects may occur if re-injection frequency occurs in intervals of four months or greater in these individuals.

The use of intramuscular injections of Botulinum neurotoxin A (BoNT-A) is indicated in a variety of conditions that cause involuntary muscle contractions. The use of BoNT-A (Botox®; Allergan, Irivne, CA) is approved by the Food and Drug Administration for the management of cervical dystonia, strabismus, hemifacial spasm, blepharospasm, glabellar lines, and primary axillary hyperhydriosis. However, off-label use for treatment of spasticity in cerebral palsy and other conditions is common. Another formulation of BoNT-A, (Dysport; Ipsen, Ltd., Slough, Berkshire,UK), is used more commonly in Europe.

The therapeutic effect of BoNT-A is due to enzymatic cleavage of SNAP-25, VAMP, and Syntaxin resulting in impaired docking of the acetylcholine vesicles to synaptic neuronal membrane. This results in a dose-dependent, reversible focal muscle weakness and atrophy .[1] Adverse effects are rare and can include flu like symptoms, transient fatigue and

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nausea, as well as injection site reactions, excessive weakness in the target muscle, falls, and pain.[2-5] In addition, subclinical effects such as increased jitter, increased fiber density, and occasional blocks on single-fiber electromyogram have been found in some studies.[6-9]

The most serious adverse event that can result from BoN-T injections is the development of systemic effects, manifested by generalized weakness, distant from the site of injection. While several case reports describe patients who developed systemic weakness after therapeutic BoNT-A injections[10-17]these cases appear to be difficult to predict. We describe three patients who developed severe, generalizedl weakness following a therapeutic administration of BoNT-A (Botox®) despite having tolerated similar injections on several prior occasions. We also review the literature and speculate on features that could predict distant spreading.

Case Reports

Case 1

A 16 year-old male with a history of right middle cerebral artery aneurysm rupture at age ten with resultant left hemiparesis was seen for 12 injection visits. During visits 1-10, he received injections to muscles in his left UE, and at times, his left gastroc/soleus, quadriceps, or hamstring every three to four months. Doses of Botox® ranged from 3.9-11.0 U/kg. Following his 11th injection (640 U; 11.0 U/kg into the left flexor carpi radialis, flexor carpi ulnaris, pronator teres, flexor digitorum superficialis, biceps, brachioradialis, and quadriceps muscles), he had difficulty getting on/off his bus. However, this symptom lasted only one month and had fully resolved by the time of his next injection. He had previously tolerated five injections ranging from 635-640 U (10.6-11.0U/kg) without side effects. He was re-injected four months later with 650 U (11.1 U/kg) into the same muscles. Four weeks following injection, he presented with weakness in both upper and lower extremities, dysarthria, and increased falls and gait instability. An EMG/nerve conduction study indicated a 26% decrement on repetitive stimulation. At 12 weeks post-injection, he had continued difficulty ascending stairs but was no longer falling and had regained full strength in his UE's. Acetylcholine receptor antibodies were not found.

Case 2

A 21 year-old female with a history of leukodystrophy and dystonia involving her ocular muscles and erector spinae was seen for six injection visits. She tolerated injections well during visits 1-5. Her dosage for visits 1-4 is unknown, as these injections were performed at another medical center. At the time of her 5th visit, performed in our clinic, she received Bo-NT injections (Botox®) in her bilateral erector spinae, latisimus dorsi, orbicularis oculi, and corrugator supercilli muscles (760 U; 12.5 U/kg) which were well tolerated without side effects. During her sixth visit three months later, she was treated with 760 U (13.2 U/kg) into her bilateral erector spinae and orbicularis oculi. Two weeks following this injection, she presented with increased gait instability/falling, difficulty arising from a chair, difficulty with climbing stairs, and dysphagia. She had 3-4/5 strength in proximal upper and lower extremity muscles, dilated but reactive pupils, and normal vital capacity and negative inspiratory force. EMG demonstrated mild, generalized acute denervation.. Muscle biopsy of her deltoid demonstrated fiber size variation, atrophic angulated fibers, and focal group atrophy consistent with neurogenic atrophy. She required hospitalization and inpatient rehabilitation. Her weakness resolved after six weeks, although she did not regain full function and strength for 16 weeks. Four months following this injection she received an intrathecal baclofen pump to reduce her dystonia. She has since had 8 follow-up visits for injections to her upper trapezius and/or ocular muscles (50-190 U; 0.5-3.9 U/kg) without side effects.

Case 3

A 38 year-old female with spastic left hemiparesis after right posterior fossa meningioma resection received therapeutic BoNT-A (Botox®) injections for spasticity on two occasions. Her first treatment was an injection of 700 U (7.7 U/kg) into the left biceps, brachialis, pronator teres, flexor digitorum profundus/superficialis, flexor carpi radialis, flexor carpi ulnaris, gastrocnemius/soleus, tibialis posterior, and hamstring muscles. This procedure was well tolerated without side effects. Three months later, she was re-injected with 700U (7.7 U/kg) into the left pronator teres, flexor digitorum superficialis, gastrocnemius/soleus, tibialis posterior, and hamstring muscles. Three weeks later, she presented with generalized weakness. She lost the ability to walk, had orthopnea, had difficulty keeping her eyes open, and experienced recurrent episodes of choking. She also had urinary frequency/ incontinence. Neurologic examination was notable for dysarthria, hypophonia, nystagmus, right lower facial weakness, right ptosis, bilateral tongue weakness, and palatal weakness. She had mild neck weakness, and her previously strong right had 4/5 strength throughout. She had 1-2/5 strength on the left. Urinalysis results indicated she had a UTI. EMG showed small, narrow, polyphasic motor unit potentials (MUP's) in the right frontalis, deltoid, and biceps muscles. Recruitment was reduced in the frontalis and biceps muscles and early in the deltoid. The frontalis exhibited increased insertional activity with 1+ fibrillations and positive sharp waves. These changes were consistent with acute/chronic denervation with many small, possibly nascent MUP's suggestive of botulinum toxicity. Six weeks later, she had improved dysphagia, right extremity and neck strength, but persistent dysarthria and hypophonia. One year after this episode, she was treated with 600U of BoNT (5.2 U/kg) into her left upper and lower extremities and, once again, reported generalized weakness for several days following the injection that resolved spontaneously. She has continued to be re-injected every three months with 500 U into her left upper and lower extremities without side effects.

Discussion

We describe three patients who developed widespread, systemic spread of Botox® in the setting of therapeutic injections. The remote effects on muscle were confirmed with EMG, indicating a severe, systemic adverse outcome . These individuals varied in age (16-38), gender, and diagnosis. While they differed in which muscles were injected and dose (650U-760 U; 7.7 U/kg-13.2 U/kg), they had all tolerated previous injections of similar doses, making these nearly impossible to predict. The risk for development of severe systemic weakness following therapeutic BoNT-A injections could be related to several factors: total injection dose, injection dose based on body weight (U/kg), frequency of injection visits, and patient age.

In order to attempt to determine commonalities between our cases and other cases of systemic weakenss following therapeutic BoNT-A, we performed a literature review for similar reports. The results of this review are in the Table. Three studies report systemic weakness in de novo patients following an initial injection. Duffey and Brown[14] reported UE and LE weakness in a 34 year-old male with idiopathic spastic paraparesis who received LE injections, 12 weeks apart, of 1000 U (11 U/kg) and 600 U of Dysport. Additionally, a 57 y/o female (1000U Dysport) and a 24 y/o male (300 U Botox®) with spinal cord injury received injections to the detrusor for management of neurogenic bladder . Both were noted to have generalized weakness lasting three months post-injection. Finally, McMahon described a six week period of hypotonia and generalized weakness in a 15 month-old with CP who received 100 U of Botox ® (11.5 U/kg) to his calf musculature.[18]

There are several reports that describe systemic weakness after repeated therapeutic injections with BoNT-A. Two studies have reported generalized muscle weakness and

electrophysiological changes in non-injected muscles in five female adults with dystonia, multiple sclerosis, and multiple systems atrophy.[10;11] Four of the five reported patients had received many injections (see Table) of Dysport (250-900 U) without previous side effects. Goldstein documented symptoms of mild systemic effects (fatigue, ptosis, diplopia, and dysarthria) in a 13-year-old subject with CP who received 23 U/kg of Botox® into lower extremity muscles.[15] Her symptoms resolved in six weeks, and she did not have any respiratory compromise. She had no adverse reaction to her first injection of 17 U/kg six months prior. Additionally, Howell et al.[19] documented respiratory stridor and dysphagia in a 9 year-old boy with CP following each of four injection visits treating lower extremity musculature using 20-25 U/kg (400 units) of Botox®. While this child had regular systemic effects after recurring injections, the risk of predictable systemic spread in children who have received repeated injections is not consistent across studies. One study reported contralateral weakness in a 53 year-old woman with spasticity post stroke following a fourth injection of 800 units (11 U/kg) into affected muscles in her paretic UE and LE.[20] Three previous injections of Botox ®to her UE's of 700 units (9.7 U/kg), 500 units (6.9 U/kg) and 600 units (83 U/kg) that were spaced three months apart were well tolerated. Finally, LeWitt and Trosch documented bilateral non-fatiguing ptosis in a 41 year-old female after receiving cervical injections (40-125 U of Botox®).[21] Symptoms developed after each of 12 injection visits with an onset of one to three days following injection and lasting for several days. There was no decremental response or abnormalities with repetitive stimulation with EMG and serum antiacetylcholine receptor antibodies were normal.

When choosing an appropriate injection dose for children and adolescents, the injection dose is often based on a patient's body weight.[22] The dosages used have increased over time. Pediatric doses of BoNT-A for treatment of spasticity in research studies have ranged from 1-16.6 U/kg of body weight (Botox®).[23;24] However, in the late 1990's, dose recommendations ranged from 12-16 U/kg of body weight.[25-27] A more recent study has demonstrated no serious adverse events using doses of 15-22 U/kg in children weighing less than 45 kg or in young adults weighing ≥ 45 kg who received total doses of 800-1200 U.[15] Children typically receive higher doses per kilogram of body weight than adults. As a point of reference, patients treated for dystonia typically receive doses in the range of 1.0-3.6 U/kg (70-250 total units) for a 70 kg adult.[28;29] As a result, children receive doses that are closer to the LD50 for primates (39 U/kg)[30] and may be at greater risk for developing systemic effects than adults.

Because children receive higher doses/kg than adults, many studies have examined the incidence of adverse events in children with CP. Bakheit and colleagues[31] reported a 7% rate of adverse events in a study of 1,594 treatments in 758 children. The authors concluded that adverse events were more closely related to the total dose given rather than dose based on body weight. However, a retrospective study by Willis et al[22] found an adverse event rate of 4.2 % in 929 encounters involving 261 patients. The adverse events were local and not systemic. The authors found no relationship between adverse events and: dose/kg of body weight, CP type, clinical presentation, ambulation status, or duration of treatment with BoNT-A. Additionally, a recent systematic review of randomized clinical trials examining safety of BoNT-A in children with CP found that studies reported only 35 adverse events in 882 participants (4%).[32] They noted that side effects of respiratory tract infection, bronchitis, pharyngytis, asthma, muscle weakness, urinary incontinence, falls, seizures, fever, and unspecified pain were attributed to the injection while other adverse events such as fatigue, headache, local infection, diarrhea, gastroenteritis, rash, generalized weakness and cough were not. However, the authors noted that adverse events were more frequent in children than in adults with other conditions. Patient age does not appear to be an independent risk factor developing systemic weakness following therapeutic injection. There

is a wide age range in the reported cases (9-67) with no clustering around a particular age category.

In our three reported cases, risk of developing systemic effects does not appear to be related to dose based on body weight, consistent with the findings of Willis et al.[22]. Our three patients developed systemic weakness following injections of 11.1, 13.2, and 7.7 U/kg. These doses of Botox® based on U/kg are similar to the adult case reported by Varghese-Kroll and Elvoic[20] but far less than the two pediatric cases reported by Howell et al[19] and Goldstein[15]

It may be more likely that risk for systemic effects is related to total injection dose and injection frequency. The results of our three patients would indicate that injections of greater than 600 units of Botox® with follow-up injections occurring every three months may have lead to an increased risk. Distant spread may also be mediated by botulinum toxin entry directly into the vascular system through the capillary field or venous system. Although our standard practice of aspirating for blood prior to injection likely precludes venous injection, capillary uptake likely does occur in some cases. Alternatively, the volume of fluid used for botlulinum toxin reconstitution may invluence systemic spread. Capillary uptake is likely greater when using larger doses of toxin and/or larger volumes of fluid for injections. It is difficult to compare our findings with other studies, as other authors often report a range of months for frequency of re-injection. Additionally, in their five adult cases, Bakheit et al[10]and Bhatia and colleagues[11] utilized Dysport (vs. Botox®) which has a conversion factor of approximately1:3 (1 unit of Botox®=3 units of Dysport). While the results of their cases demonstrated that lower doses of Botox ® (using this conversion factor) may result in systemic effects, the duration between injections visits was shorter, making it difficult in these cases to determine if symptoms were due to injection dose or re-injection frequency. Further studies that examine total injection dose and re-injection frequency are recommended.

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Table 1

Summary of reported cases of botulism after therapeutic injection

Study	Age/Gender/Dx	Muscles Injected (EMG guidance)	Total Dose-U (Dose/kg)	Dilution	Adverse Reaction /Symptoms	Symptom Duration (symptom onset from injection)	Number of previous injections (duration between injections)	EMG confirmed findings (Y/N)
Bakheit AM, Ward CD, McLellan DL 1997	67/F/MS with spastic paraparesis	Left HS (N/A)	250 **Dysport** (unknown)	Unknown	Dysphonia, generalized weakness, ptosis	4 weeks (4 days)	None	Y
	34/F/MSA	Right SCM, Left splenius capitis, Left middle trapezius (N/A)	750 **Dysport** (unknown) *[Ø]*	Unknown	Dysphagia, dysarthria, diplopia, and weakness of neck/trunk/limbs	4 months (3 weeks)	Every 2-3 months for 5 years (2-3 months)	Y
Bhatia KP, Munchau A, Thompson PD et al. 1999	45/F/CD	Right SCM, Bilateral splenius capitis (N/A)	650 **Dysport** (unknown)	Unknown	Visit 1995: fatigue, limb weakness Visit 1996: Proximal UE weakness, nasal regurgitation, dysphagia	4 weeks (1 week) 9 months (1 week)	Every 12-14 wks for prev. 6 yrs Every 12-14 wks for prev.7 yrs	N Y
	57/F/ hemidystonia	Left biceps, brachioradialis, FCU, adductor pollicis (N/A)	900 **Dysport** (unknown)	Unknown	Fatigue and weakness in both extremities	1 month (14 days)	9 (10-12 weeks)	Y
	32/F/ hemidystonia	Left FHB, FDB, soleus, and FDL (N/A)	Injection # 8: 600 **Dysport** (unknown) Injection # 9: 800 **Dysport** (unknown)	Unknown Unknown	UE > LE weakness, dysphagia, asymmetric ptosis, dysarthria UE > LE weakness, dysphagia	3 months (1 week) 2 months (10 days)	7 (8-10 weeks) 8 (N/A)	N Y
McMahon M. 2002	15-month / M / CP	Bilateral gastrocnemius (N/A)	100 **Botox** (11.5 U/kg)	100 U : 1ml	UE hypotonia, generalized weakness, poor feeding	6 weeks (2 days)	None	N/A
Wyndaele JJ, Van Dromme SA. 2002	57 / F / SCI neurogenic bladder 24 / M / SCI neurogenic bladder	Detrusor (N/A) Detrusor (N/A)	1000 **Dysport** (N/A) 300 **Botox** (N/A)	N/A	Generalized weakness Generalized weakness	3 months (N/A) 3 months (2 weeks)	1 (3 months) None	N/A N/A
Duffey P, Brown C. 2006	34 / M / Idiopathic spastic paraparesis	Bilat. Gastroc. and right tibialis post.	1000 **Dysport** (11 U/kg) 12 wks	N/A N/A	Fatigue, UE, LE weakness after both injection	Unknown (2 weeks)	None	N/A

Study	Age/Gender/Dx	Muscles Injected (EMG guidance)	Total Dose-U (Dose/kg)	Dilution	Adverse Reaction /Symptoms	Symptom Duration (symptom onset from injection)	Number of previous injections (duration between injections)	EMG confirmed findings (Y/N)
		(No EMG)	later=2nd inj. of 600 U		doses			
Goldstein EM 2006	13/F/CP 10/M/CP	Bilateral HS and gastroc/soleus (N/A) Bilateral Hamstrings (N/A)	Unknown **Botox** (23 U/kg) Unknown **Botox** (18U/Kg)	Unknown Unknown	Fatigue, ptosis, diplopia, and dysarthria *[†]* Leg weakness, slow ambulation	6 wks 6 weeks (unknown)	1 (6 mos) Unknown	N N
Howell K, Selber P, Graham HK, Reddihough D. 2007	9/M/CP	Bilateral HS, adductors, gastroc/soleus (No EMG)	400 Botox (20-25 U/kg)	2ml	Vomiting, hematemesis, stridor, and labored breathing, dysphagia	Symptoms occurred after each injection and never completely resolved between them. (1 day)	4 (4-7 mos)	N
Varghese-Kroll E, Elovic EP. 2009	53/F/CVA	Visit 4=15 muscles in left UE/LE (under EMG guidance) Visit 8=9 muscles in left UE (under EMG guidance)	800 **Botox** (11 U kg) *[Ø]* 500 **Botox** (6.9 U/kg)	1 ml 1 ml	Fatigue and contralateral weakness *[†]*	3 weeks (N/A) 4 weeks (4 weeks)	Unclear, multiple (3 months) Unclear, multiple (3 months)	N
Crowner BE, Torres-Russotto D, Carter AR, and Racette BA	16/M/CP	Visit 11=left HS, RF, and 6 UE muscles Visit 12=left HS, RF, and 6 UE muscles	640 **Botox** (11.0 U/kg) 650 **Botox** (11.1 U/kg)	1 ml	Increased falling/gait instability, progressive weakness of unaffected extremities, dysarthria	12 weeks	11 (3-4 mos.); difficulty stepping onto a bus x1 mo.	Y
	21/F/dystonia, leukodystrophy	Bilateral erector spinae and orbiularis oculi	760 **Botox** (13.2 U/kg)	1 ml	LE weakness, falling, headache, abdominal pain, shallow breathing and weak cough	6 weeks	5 (3-4 mos)	Y

Study	Age/Gender/Dx	Muscles Injected (EMG guidance)	Total Dose-U (Dose/kg)	Dilution	Adverse Reaction /Symptoms	Symptom Duration (symptom onset from injection)	Number of previous injections (duration between injections)	EMG confirmed findings (Y/N)
	38/F/Right meningioma resection	Left pronator teres, FDS, gastroc/soleus tibialis post., and HS	700 **Botox** (7.7 U/kg)	Unknown	Generalized weakness, dysphagia, dysarthria, diplopia, orthopnea and dyspnea on exertion	1 month; dysarthria/ dysphagia lasted longer	1 (3 mos)	Y

[Ø] Patient had received previously same or higher doses without side effects.

[†] Patient underwent subsequent chemodenervation procedures without complications.

N/A = no information provided.