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Yasuhiko Baba, M.D.[1], Michael D. Osborne, M.D.[2], Zbigniew K. Wszolek, M.D.[1] Andrzej Kwolek M.D.[3], Mariusz Drużbicki Ph.D.[3]

[1] Department of Neurology, Mayo Clinic Jacksonville, FL, USA,
[2] Department of Physical Medicine & Rehabilitation, Mayo Clinic Jacksonville, FL, USA,
[3] Institute of Physiotherapy University of Rzeszow Poland

Treatment of Spasticity with Botulinum Toxin

Key words: *upper motor neuron, multiple sclerosis, brain injury, spinal cord injury, cerebral palsy, stroke*

SUMMARY

Spasticity is a complex disorder characterized by a velocity-dependent increase in muscle tone associated with exaggerated deep tendon reflexes. It can be caused by numerous diffuse or focal cerebral and spinal pathologic conditions. Spasticity indicates upper motor neuron dysfunction and if severe, can lead to considerable motion restriction and eventually to more serious disability.

The therapeutic interventions available to treat spasticity are often of limited benefit. In the last decade, many open-label and several double-blind, placebo-controlled, studies have demonstrated the effectiveness of intramuscular botulinum toxin (BTX) injections for the management of spasticity caused by multiple sclerosis, brain / spinal cord injury, cerebral palsy, and stroke. BTX can also be beneficial in the treatment of spasticity, or a mixture of spasticity and rigidity, in many neurodegenerative conditions; including Parkinson disease, progressive supranuclear palsy, corticobasal degeneration, frontotemporal dementia and parkinsonism linked to chromosome 17, and in various sporadic and familial spinocerebellar ataxia syndromes.

Currently, two BTX serotypes, which are serologically different but share a common subunit structure, are commercially available: type A (Botox®, manufactured by Allergan, Inc, Irvine, California, USA; and Dysport®, distributed by Beaufour-Ipsen Pharmaceuticals, Paris, France); and type B (manufactured by Elan Corporation, Dublin, Ireland, and available in the United States as MyoBloc® and in Europe as NeuroBloc®). BTX primarily affects the neuromuscular junction by inhibiting acetylcholine release. Dosages vary considerably depending on the particular preparation used, the muscle injected, the severity of the condition, and the duration of treatment.

INTRODUCTION

Spasticity is a motor disorder characterized by a velocity-dependent increase in tonic stretch reflexes (muscle tone) with exaggerated tendon jerks. It results from hyperexcitability of the stretch reflex, and is one component of the upper motor neuron syndrome [1]. Various conditions such as cerebral palsy, stroke, brain injury, spinal cord injury, and multiple sclerosis involve dysfunction of the central nervous system (CNS) and are associated with spasticity. Prior to 1989, management strategies of spasticity were limited to physical treatment regimens, oral anti-spastic agents, and surgical approaches. With the commercial development of botulinum toxin (BTX) – a novel approach to spasticity management was introduced.

BTX is a potent and potentially lethal toxin produced by the gram negative anaerobic bacterium Clostridium botulinum. Its first therapeutic use was in the treatment of paralytic strabismus and blepharospasm by Alan B. Scott and Edward J. Schantz [2]. The United States Food and Drug Administration (FDA) approved BTX type A for clinical use in 1989. Since then there has been a considerable increase in its popularity in the treatment of a wide variety of dystonic and non-dystonic disorders associated with spasticity. In the past decade, many open-label and several double-blind, placebo-controlled, studies have demonstrated the effectiveness of BTX as a treatment for spasticity. BTX exhibits its effect through a selective and reversible inhibition of neurotransmission in the neuromuscular junction. It has evolved into a new and effective alternative treat-

ment strategy for spasticity. Recently, BTX type A has been licensed for the treatment of spasticity in many European countries, and its popularity is rapidly expanding.

In this review, we discuss the pharmacology of BTX, and its role in the management of spasticity. Moreover, we explore its possible applications in the treatment of neurodegenerative conditions with mixed spasticity and rigidity.

SPASTICITY

Spasticity may result from diffuse or focal CNS pathologies, including stroke, brain/spinal cord trauma, anoxic/metabolic encephalopathy, multiple sclerosis, cerebral palsy, and other neurodegenerative disorders. The temporal profile and natural history are different in each individual with spasticity but the clinical phenomena associated with the upper motor syndrome have a common pathophysiology [3].

The clinical syndrome of spasticity usually develops several weeks after the occurrence of a CNS lesion. When injury or disease involves the corticospinal tracts, paresis and secondary muscle shortening (contracture) often occur. Muscle shortening alone may be the first generator of spasticity [4-6]. The delayed rearrangement of spinal reactivity that results from CNS damage leads to abnormal muscle contractions and reflex responses. These alterations are the basic pathophysiology of spasticity. Spasticity and other types of muscle overactivity then propagate further contracture formation. [6].

Impaired movement, weakness, painful muscle spasms, and stiffness typically accompany spasticity.

Tab. 1. Treatment strategies for spasticity

Rehabilitation
• Physical therapy
• Occupational therapy
• Adaptive equipment (bracing, orthoses)
• Serial casting
• Electrical stimulation
Oral medications
• Baclofen*
• Tizanidine*
• Diazepam*
• Dantrolene*
• Clonidine
• Clonazepam
• Clorazepate
• Ketazolam
• Piracetam
• Progabide
• Cyproheptadine
Intravenous medications
• Orphenadrine
• Thymoxamine
Intrathecal medication
• Baclofen
Focal chemodenervations
• Ethyl alcohol
• Phenol
• Botulinum toxin
Surgeries
• Selective dorsal rhizotomy
• Orthopedic surgery (tenotomy)

*US Food & Drug Administration approved for the treatment of spasticity

These impairments result in functional limitations with self-cares, hygiene, dressing, transfers, sitting, mobility, and walking. Severe or long-duration spasticity often leads to joint ankylosis. Profound limitations in mobility may lead to skin breakdown and decubitus ulceration.

Numerous interventions exist for the treatment of spasticity (Table 1). [7-8]. However, the effectiveness of these methods varies greatly. Rehabilitation methods alone are generally more successful for mild spasticity. Though oral medications are more successful in alleviating moderate to severe-spasticity, side effects may limit their uses. Neurolytic and surgical procedures are effective, yet irreversible, and may lead to eventual functional deterioration.

BOTULINUM TOXIN

Clinical Pharmacology

More than a century ago, a toxin-producing bacterium called Bacillus botulinus (later named Clostridium botulinum) was first detected [9]. Thus far, seven immunologically distinct serotypes of BTX (A-G) have been identified [10]. The toxin is a 150 kDa molecular weight protein which consists of a heavy chain (100 kDa) and a light chain (50 kDa) [11]. The C-terminal region of the heavy chain binds to the surface of target nerve cells and inhibits the release of acetylcholine at the presynaptic cholinergic nerve terminal [12]. This neurotransmitter blocking mechanism results in a chemical denervation that reduces the force of voluntary and involuntary muscle contractions [13].

Serotypes

BTX type A binds to a 25 kDa synaptosome-associated protein (SNAP-25) and inhibits the calcium-mediated release of acetylcholine [14]. BTX type E also binds SNAP-25 but the target cleavage site in the carboxyl-terminal region of SNAP-25 differs from those of BTX type A [14]. BTX type B, D, F and G cleave the cellular substrate of vesicular-associated membrane protein (VAMP) [13]. BTX type C acts by binding to syntaxin and SNAP-25 [15, 16]. Among these serotypes, BTX type A and BTX type B are commercially available for clinical use. Botox® (Allergan, Inc., California) and Dysport® (Ipsen, Inc., United Kingdom) utilize serotype A, and MyoBloc® (Elan, Inc., New York) utilizes serotype B. Although Botox® and Dysport® are purified from same serotype, there are significant differences between the potencies of these products a witha Dysport®/ Botox® equivalency ratio of approximately 3: 1 to 4: 1 [13,17].

BOTULINUM TOXIN THERAPY FOR SPASTICITY

Indication

In the United States BTX has been approved for use in cervical dystonia (Botox® and MyoBloc®), and for strabismus, blepharospasm, and other facial nerve disorders (Botox®). Off label applications have expanded to numerous additional disorders associated with spasticity such as stroke, spinal cord injury, and cerebral palsy.

BTX is indicated for the treatment of moderate to severe spasticity that has not responded to more conservative therapies such as stretching, bracing and oral medications. Appropriate patient selection is the key to a successful outcome from BTX injection. The ideal candidate has focal areas of spasticity, which cause functional impairment, or limit self-cares and hygiene. Examples include equinovarus deformity of the foot, common to stroke patients; and hip adduction spasticity, common to individuals with cerebral palsy. BTX is not effective in treating diffuse hypertonicity. Additionally, patients with severe fixed contractures, bony torsion and joint instability, are poor candidates [18].

In pediatric patients, the timing of BTX therapy is vital because BTX therapy during the dynamic phase of motor development may provide longstanding reductions in muscle tone [18]. It is generally recommended that BTX injection in children be accomplished in the upper extremity at greater than four years of age, and in the lower extremity between one and five years of age to obtain maximal response [18]. Though BTX has been used in clinical studies involving children, as of this date, Botox® and MyoBloc®, have not been approved by the FDA for use in pediatrics.

Therapeutic Usage

The dosages of Botox® for a variety of target muscles in adult and children with spasticity are shown in Table 2 [19-28]. The number of injection sites differs by a function of muscle size and ease of access [23]. The dosage is also determined by functional state, muscle bulk, and the number of muscles injected simultaneously [22, 23].

Goals of Management

It is important to outline and prioritize treatment goals of spasticity management. Common treatment goals are listed in Table 3. A variety of scales and measures can be useful in documenting the outcome of BTX therapies: Selective Motor Control Scale

Tab. 2. Therapeutic usage of botulinum toxin type A (Botox®) for spasticity*

		Adults	Children
Upper Limbs			
Adducted/internally rotated shoulder	Pectoralis Major	75-150U	2U/kg
	Latissimus Dorsi	50-150U	2U/kg
Flexed elbow	Biceps Brachii	25-200U	2U/kg, 40-62U
	Brachialis	25-100U	2U/kg, 40-62U
	Brachioradialis	15-100U	1U/kg, 30-40U
Pronated forearm	Pronator Teres	20-75U	1U/kg, 12-19U
Flexed wrist	Flexor Carpi Radialis	5-100U	1-3U/kg, 13-47U
	Flexor Carpi Ulnaris	10-75U	1-3U/kg, 16-35U
Thumb-in-palm deformity	Flexor Pollicis Longus	5-25U	1-3U/kg, 5-40U
	Adductor Pollicis	5-25U	1U/kg
Clenched fist	Flexor Digitorum Profundus	5-120U	1-2U/kg, 20-39U
	Flexor Digitorum Superficialis	5-150U	1-3U/kg, 19-50U
Lower Limbs			
Flexed hip	Iliacus	50-100U	1-2U/kg
	Rectus Femoris	50-200U	3U/kg, 75-100U
Flexed knee	Medial Hamstrings	40-150U	3-6U/kg, 69-96U
	Lateral Hamstrings	100-200U	2-3U/kg
	Gastrocnemius	50-150U	3-6U/kg, 64-92U
	Vastus Lateralis	60U	2-3U/kg
Adducted thighs	Adductor Longus/Brevis/Magnus	50-300U	3-6U/kg, 60-84U
Stiff knee	Quadriceps	50-200U	3-6U/kg
Equinovarus foot	Gastrocnemius	50-200U	3-6U/kg, 64-92U
	Soleus	50-100U	2-3U/kg
	Tibialis Posterior	40-200U	1-2U/kg, 50-62U
	Tibialis Anterior	30-150U	1-3U/kg, 25-70U
	Flexor Digitorum Longus/Brevis	40-150U	1-2U/kg
	Flexor Hallucis Longus	25-75U	1-2U/kg
Striatal toe	Extensor Hallucis Longus	20-100U	1-2U/kg, 30U

*Adapted from refs [19-28]

[18, 29], Physician's Rating Scale [18, 30, 31], Gross Motor Function Measure [32], Pediatric Evaluation of Disability Inventory [33], Modified Ashworth Scale [34].

Therapy failure

Some patients who undergo BTX injections experience therapy failure. BTX therapy failure has been classified into primary failure and secondary failure [35]. Primary therapy failure includes inappropriate patient selection (ie. selection of subjects with disorders which are insensitive to BTX, such as fixed joint contracture). Other causes of primary failure include technical problems, such as inappropriate target muscle selection or injection of inadequate BTX dosage [35,36]. Therapy failure due to antibody production is termed secondary failure. After initiating BTX therapy, complete antibody-related therapy failure has been reported to occur between 11 months (3 to 4 injection series) and 58 months (11 to 12 injection series) [35,37]. These findings suggest that the frequency and dosage of BTX are not directly correlated with antibody-related therapy failure [35]. Some have proposed that a „drug holiday" may provide renewed efficacy for patients suffering from antibody-related therapy failure. However, there is no evidence demonstrating the effectiveness of this management strategy. To reduce the development of

antibodies the minimal recommended interval between injection series is considered to be 3 months [18]. Antibody-related therapy failure can be easily observed when a patient fails to develop paresis following superficial muscle injection (such as the frontalis or levator palpabrae) [38]. Antibodies to BTX type A can also be documented by radioimmunoassay [39].

Adverse Effects

The frequency of adverse effects (AE) accompanying BTX therapy is shown in Table 4 [19, 28, 40-43]. Treatment-related AE are usually mild; life-threatening and fatal events are extremely rare. AE usually occur between 1 and 25 days post-injection and lasts about 1 to 2 months [42,43].

Tab. 3. Goals of botulinum toxin therapy*

• Decrease spasms (tone)
• Improve mobility
• Decrease pain
• Increase range of motion
• Decrease evolution of contractures
• Delay or prevent surgery
• Reduce the need for oral medications
• Improve orthoses fit
• Facilitate rehabilitative therapies
• Improve positioning
• Improve cosmetic appearance

*Adapted from Ref. [8, 54]

Tab. 4. The frequency of adverse effects accompanying botulinum toxin (BTX) therapy

BTX type A
• Hypertonia (22%)
• Pain (3-8%)
• Fatigue (1-7%)
• Headache (5-6%)
• Dizziness (6%)
• Muscle weakness (3-6%)
• Incoordination (5%)
• Urinary tract infection (5%)
• Diarrhea (5%)
• Ecchymosis (3%)
• Local infection (3%)
• Hyposthesia (1%)
BTX type B
• Dry mouth (90%)
• Pain (10%)
• Affected arm heaviness (10%)

Ref. [19, 28, 40-43]

Results of Randomized Control Trials

Several large randomized control trials (RCT) regarding efficacy of BTX type A for spasticity have been reported (Table 5) [28, 40, 44-50]. The etiology of spasticity of the subjects in these RCT varies, though most of the studies were conducted in patients with stroke. Bakheit et al [46] performed a randomized control trial evaluating the efficacy of 500U, 1000U or 1500U of Dysport® for upper extremity spasticity in 83 patients with stroke. In this study, a moderate to marked improvement in Modified Ashworth Scale were seen in 68% cases of the 500U group, 73% cases of the 1000U group, and 53% cases of the 1500U group at 4 weeks post injection. Brashear et al [28] reported a randomized clinical trial evaluating the efficacy of Botox® (range of dose: 200-240U) for upper extremity spasticity in 126 patients with stroke. Using the Modified Ashworth Scale, wrist flexor tone improved by 53% at 6 weeks and 34% at 12 weeks post injection; finger flexor tone improved by 44% at 6 weeks and 26% at 12 weeks post injection. Hyman et al [40] completed a randomized clinical trial evaluating the efficacy of 500U, 1000U or 1500U of Dysport® for lower extremities spasticity in 74 patients with multiple sclerosis. Assessment at 4 weeks post injection, demonstrated that Modified Ashworth Scale improved by 53% in the 500U group, 25% in the 1000U group, and 43% in the 1500U group.

In a randomized clinical trial in pediatric patients, Koman et al [41] reported the efficacy of BTX type A in 114 children with equinus gait due to cerebral palsy. Four U/kg of Botox® was injected in the lower extremity. The Physician Rating Score response rate was significantly greater in the BTX type A group (61%) compared to placebo group (25%) at 8 weeks after injection.

Recently, a 12-week, randomized clinical trial evaluating the efficacy of MyoBloc® for spasticity was reported [42]. In a double-blind assessment using the Modified Ashworth Scale, wrist flexor tone improved by 69% in the BTX type B (10000U) treated group at 2 weeks following injection, which was statistically significant compared to the placebo group. However, the improvement of wrist flexor tone at other follow up visits and improvement in Modified Ashworth Scale in elbow, finger and thumb were not significantly different between the BTX type B and placebo groups.

Further Application of Botulinum Toxin Therapy

The efficacy and safety of BTX therapy is supported by the several RCTs previously cited, and suggests that BTX can be a new and effective therapeutic tool for patients with spasticity associated with a variety of conditions. Recently, the effect of BTX type A in the treatment of spasticity due to HIV-associated encephalopathy has been reported [51]. BTX has also been used in patients with amyotrophic lat-

Tab. 5. Recent Randomized Controlled Studies involving botulinum toxin type A treatment for spasticity

Study	N	Subjects	Follow-up	Target extremities	Treatment dose	Results (quantitative assessment)*, **
Burbaud et al (1996)	23	Stroke, head trauma	90 days	L/E	Dysport®: 200-1000U	35% in ASH ankle extensors 36% in ASH ankle invertors 50% in active ankle dorsiflexion
Simpson et al (1996)	39	Stroke	16 weeks	U/E	Botox®: 57, 150 or 300U	46% in ASH wrist flexor at 6 weeks 42% in ASH elbow flexor at 6 weeks
Bakheit et al (2000)	82	Stroke	16 weeks	U/E	Dysport®: 500, 1000 or 1500U	Moderate to marked improvement of ASH in 68% of 500U, 73% of 1000U, and 53% of 1500U group at 4 weeks
Hyman et al (2000)	74	Multiple sclerosis	12 weeks	L/E	Dysport®: 500, 1000 or 1500U	53% in ASH in 500U group at 4 weeks 25% in ASH in 1000U group at 4 weeks 43% in ASH in 1500U group at 4 weeks 50% in HA in 1000 and 1500U groups at 4 weeks
Bhakta et al (2000)	40	Stroke	12 weeks	U/E	Dysport®: 1000U	30% in ASH finger flexor at 6 weeks 25% in ASH elbow flexor at 2 weeks
Richardson et al (2000)	52	Stroke, head trauma, spinal cord injury, tumor, cerebral palsy, anoxic brain	12 weeks	U/E or L/E†	Botox®: 30-305U in U/E, 75-500U in L/E	43% in ASH at 3 weeks
Bakheit et al (2001)	58	Stroke	16 weeks	U/E	Dysport®: 1000U	Moderate to marked improvement in ASH in 52% at 4 weeks
Brashear et al (2002)	126	Stroke	12 weeks	U/E	Botox®: 200-240U	53% & 34% in ASH wrist flexor at 6 and 12 weeks, respectively 44% & 26% in ASH finger flexor at 6 and 12 weeks, respectively 37% in ASH thumb flexor at 12 weeks
Pittock et al (2003)	234	Stroke	12 weeks	L/E	Dysport®: 500, 1000 or 1500U	Greatest improvement in ASH in 1500U group at 4, 8 and 12 weeks Improvement of ASH in 500 and 1000U groups at 4 weeks

*Results other than studies of Bakheit et al (2000, 2001) and Pittock et al (2003) indicate % improvement from baseline in treated group(s).
**Included data show statistically significance compared to those of placebo.
†Botulinum toxin type A was injected in U/E of 32 cases and L/E of 20 cases.
ASH = Ashworth scale, L/E = lower extremity, N = number of patients, U/E = upper extremity

eral (ALS) sclerosis who were unable to open their mouths as a consequence of spasticity [52]. Restivo et al [53] reported that BTX type A injections in the bilateral masseter muscles were beneficial for ALS patients who cannot undergo feeding tube placement because of spastic closure of the mouth.

Grazko et al [20] reported that BTX type A intramuscular injection showed significant reduction of rigidity along with functional improvement in patients with progressive supranuclear palsy, corticobasal degeneration and Parkinson's disease. The effect lasted for an average of 3.4 months (range: 1 to 4.5 months). These findings suggest that BTX can also be beneficial in the treatment of the mixed spasticity and rigidity common to many neurodegenerative conditions. However, further large-scale RCT are necessary to establish efficacy of BTX in the treatment of patients with rigidity/spasticity unresponsive to medication therapies.

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Address for correspondence
Zbigniew K. Wszolek, M. D.
Department of Neurology,
Mayo Clinic Jacksonville
e-mail: wszolek.zbigniew@mayo.edu

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