

Treatment With Botulinum Neurotoxin of Gastrointestinal Smooth Muscles and Sphincters Spasms

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Abstract: Local injections of botulinum neurotoxin are now considered an efficacious treatment for neurological and non-neurological conditions. One of the most recent achievements in the field is the observation that botulinum neurotoxin provides benefit in diseases of the gastrointestinal tract. Botulinum neurotoxin inhibits contraction of gastrointestinal smooth muscles and sphincters; it has also been shown that the neurotoxin blocks cholinergic nerve endings in the autonomic nervous system, but it does not block nonadrenergic responses mediated by nitric oxide. This aspect has further promoted the interest to use botulinum neurotoxin as a treatment for overactive smooth muscles, such as the anal sphincters to treat anal fissure and outlet-type constipation, or the lower esophageal sphincter to treat esophageal achalasia. Knowledge of the anatomical and

functional organization of innervation of the gastrointestinal tract is a prerequisite to understanding many features of botulinum neurotoxin action on the gut and the effects of injections placed into specific sphincters. This review presents current data on the use of botulinum neurotoxin to treat diseases of the gastrointestinal tract and summarizes recent knowledge on the pathogenesis of disorders of the gut due to a dysfunction of the enteric nervous system. © 2004 Movement Disorder Society

Key words: anus; physiopathology; autonomic nervous system diseases; botulinum toxin; therapeutic use; enteric nervous system; esophageal achalasia; esophageal diseases; exocytosis; fissure-in-ano; gastric emptying; gastrointestinal motility; membrane fusion; membrane proteins; neuromuscular agents; spasm

After the discovery that botulinum neurotoxins (BoNT) inhibit neuromuscular transmission, the range of clinical applications has grown to encompass several neurological and non-neurological conditions. Over the years, the number of primary clinical publications has grown exponentially and continues to increase every year. One of the most recent discoveries is the observation that injections of BoNT ameliorate diseases of the gastrointestinal tract (GIT). BoNT is not only potent in blocking skeletal neuromuscular transmission but also in blocking cholinergic nerve endings in the autonomic nervous system.¹ The capa-

bility of BoNT to inhibit contraction of GIT smooth muscles, first based on in vitro and later on in vivo observations, has been shown to be due to inhibition of acetyl choline (ACh) release rather than affecting contractions mediated by nitric oxide (NO).² This finding has further promoted the interest to use BoNT as a treatment for overactive smooth muscles and sphincters, such as the lower esophageal sphincter (LES), to treat achalasia, or for the anal sphincters, to treat anal fissure and outlet-type constipation.

Information on the anatomical and functional organization of GIT innervation is a prerequisite to understanding many features of BoNT action on the GIT and the effects of injections placed into specific sphincters. This review presents current data on the use of BoNT to treat GIT diseases and summarizes recent knowledge on the pathogenesis of GIT disorders due to a dysfunction of the enteric nervous system (ENS).

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PROPERTIES OF THE GIT SMOOTH MUSCLES

Smooth muscle contraction is regulated by changes in cytosol calcium levels.³ Calcium regulation is affected by a variety of regulatory proteins; relaxation of smooth muscles occurs when there is a resulting decrease in cytosolic calcium, while contraction is dependent on an increase in cellular calcium. The precise mechanisms responsible for the maintenance of smooth muscle tone are still not entirely known. These functions depend on the intrinsic electrical and mechanical properties of GIT smooth muscles and are regulated by the ENS and by sympathetic and parasympathetic influences. Hormones also regulate muscle activity and influence GIT motility.^{4,5} Interstitial cells of Cajal act as local pacemakers to generate the rhythmic activity of the circular muscle layer throughout the GIT. Motor neurons control the musculature indirectly, through their action on Cajal's cells.⁵ Substances, such as histamine, serotonin, adenosine, and eicosanoids, produced by non-neural cells, can influence smooth muscle activity.

At the esophageal level, muscle tone of the LES results from the interaction of neurogenic and myogenic effects.^{4,6} Neurogenic tone in humans is partly due to cholinergic innervation; various other excitatory and inhibitory neurotransmitters are present in the sphincter, but their physiologic importance is unclear. The modulation of LES tone is largely mediated through the vagus nerve.⁴ ACh is the presynaptic neurotransmitter; postsynaptic transmission is mediated by NO, but vasoactive intestinal polypeptide (VIP) is also thought to contribute.⁵⁻⁷

At the anal level, the sphincter complex consists of two overlapping sphincters.^{3,8-11} The external anal sphincter (EAS), that forms the outer layer, is composed of a voluntary, striated, skeletal muscle. The internal anal sphincter (IAS) is the inner, involuntary, smooth muscle component. It is in a state of continuous maximal contraction, due to a combination of intrinsic myogenic and autonomic neurogenic properties.⁵ Being of visceral origin, IAS is supplied both by sympathetic and parasympathetic nerves; in addition, the ENS modulates its tonic activity.^{5,7} Noradrenergic sympathetic nerves are considered excitatory and the parasympathetic inhibitory to the IAS. Vagal neurons do not act directly but rather form synaptic connections with neurons whose cell bodies are in the intrinsic GIT ganglia. This transmission is principally mediated by ACh acting on nicotinic receptors.⁵ Recently, it has been shown that the longitudinal layer and the circular smooth muscle in the human rectum

receive an intrinsic NO-mediated inhibitory innervation.¹²⁻¹⁴

ORGANIZATION OF THE ENS

Motility of a gut segment depends on its extrinsic and intrinsic innervation.^{5,15} Preganglionic parasympathetic nerves and postganglionic sympathetic nerves, which constitute the autonomic nervous system, provide extrinsic innervation; the ENS provides the intrinsic innervation.⁵ It is a highly complex system, responsible for the coordination of motility in the GIT. The ENS can function independently of the central nervous system (CNS), which nevertheless maintains a coordinating role for diverse functions of GIT neurons by means of sympathetic and parasympathetic motor and sensory pathways.^{4,5} A deficiency of enteric neurons causes obstruction and lack of intestinal propulsion.

The ENS is composed of two main ganglionated plexuses: Auerbach's myenteric plexus and Meissner's submucous plexus. Other, nonganglionated, plexuses, such as the longitudinal muscle plexus, the circular muscle plexus, the plexus of the muscularis mucosae, and the mucosal plexus, supply GIT layers. Intraparietal neurons encompass motor neurons (excitatory and inhibitory), interneurons, and intrinsic sensory neurons. Sympathetic and parasympathetic neurons also innervate the GIT. ACh is the primary excitatory transmitter. Inhibitory motor neurons relax smooth muscles; these neurons release a combination of at least three transmitters: NO, adenosine triphosphate, and VIP.

Sympathetic pathways to the GIT are noradrenergic; they inhibit motility, constrict the sphincters and in general inhibit contractile activity. The vagus nerve is involved in complex circuits integrating various enteric reflexes with signals that derive from the CNS and from other GIT regions; ACh principally mediates this transmission.⁵

APPLICATION IN THE LOWER GIT

Chronic Anal Fissure

This is a cut or crack in the anal canal or anal verge that may extend from the muco-cutaneous junction to the dentate line.^{8,16,17} It shows great reluctance to heal without intervention. Classic symptoms are pain on or after defecation that is often severe and may last from minutes to several hours. Often there is bright blood on the toilet paper. The majority of fissures occur in the posterior midline of the anal canal; fissures are located in the anterior midline in 10% of women and 1% of men. Multiple fissures or lateral fissures raise suspicion of other diseases, including inflammatory bowel diseases,

human immunodeficiency virus, or syphilis.¹⁸ The fissure can be seen as the buttocks are parted. It is often suspected because there is marked anal spasm making examination difficult.

The cause of chronic fissures and the reasons for their failure to heal remain unclear. Also unexplained are the main characteristics of this painful condition, including the predilection for posterior midline and the lack of granulation tissue at the fissure site. Several theories have been advanced to unravel the underlying cause of anal fissure. By using laser Doppler flowmetry, it has been shown that the posterior area of the anoderm is less well perfused than other areas of anoderm. There is speculation that increased IAS tone further reduces the blood flow, especially at the posterior midline. Based on these findings, fissures are thought to represent ischemic ulceration. Trauma during defecation is believed to initiate the formation of a fissure. The trauma can be the result of passage of a hard, constipated stool or explosive diarrhea. Fissure is associated with childbirth in 3 to 11% of patients. Shearing forces from the fetal head on the anal mucosa or mucosal tethering after childbirth rendering it more susceptible to trauma have both been incriminated.

IAS spasm has been noted for many years in association with anal fissure; thus, surgical treatment has been generally aimed at overcoming the spasm. It has been found that the IAS of patients with anal fissure is fibrotic, compared with that of controls.¹⁹ It was then postulated that a myositis might occur early in the course of a fissure and that this condition is the underlying cause of both spasm and fibrosis.

Decreased anodermal blood flow may be promoted by endothelial cell dysfunction associated with reduced NO synthesis, which is known to be involved in the regulation of local blood flow. Interruption of the endothelial continuity does not only remove the anticoagulant and vasodilator functions of the endothelium, but it also exposes the subendothelium that has several procoagulant functions. These changes may be induced by inflammatory or immune cytokines. Activation of the endothelium may express antigens as the endothelial cells can act as antigen-presenting cells. Anti-endothelial cell antibodies have been found in many patients with anal fissure but not in healthy controls.²⁰ In antibody-positive patients, higher resting anal tone has been observed. A primary IAS disturbance may be a contributing etiologic factor. IAS supersensitivity to β -agonists has been observed in the patients with chronic fissure.²¹ This finding may be induced by a prolonged absence of the neurotransmitter, by abnormalities at neurotransmitter or metabolic level, or by a modification of cholinergic and

adrenergic receptors. Increased IAS adrenergic or cholinergic activity is likely to occur in chronic fissure, as demonstrated by the efficacy of BoNT in inducing fissure healing and reduction of resting tone after injection into the IAS.^{22,23}

Conventional Therapies.

Because the passage of a hard stool is thought to contribute to the development of anal fissure, the control of constipation has been considered the main treatment for years.¹⁸ Dilators have been used for many years. They have been criticized as being merely a way of applying an anesthetic ointment. If symptoms fail to resolve or have been present for a long period of time, resolution without surgery becomes increasingly less likely. Lateral internal sphincterotomy (LIS) has been the most commonly used treatment for chronic fissure since the 1950s.^{8,18} The results of LIS have been reported from many centers. Although LIS heals and relieves symptoms of chronic fissure in nearly all patients (96%), the incidence of incontinence varies.²⁴ The largest studies report impairment of continence in up to 30% of patients. Although most episodes of incontinence are minor and transient, in a subset of patients, incontinence is permanent.

Results of BoNT Treatment.

BoNT can be used to treat anal fissure (Table 1).^{25–29} BoNT injection into the internal sphincter close to the fissure was first described in 1993. Since then, this modality has gained popularity as a treatment for chronic fissure. In a recent study, BoNT anterior injection was associated with earlier healing of a posterior fissure than was posterior injection. The optimal BoNT dose is unclear. The therapeutic efficacy of different doses have been reported recently.^{23,26,27} It has been found that the healing rate does not differ significantly when the total dose and the number of injection sites are varied. In a recent study, the influence of different dosage regimens injected anteriorly in the IAS on the clinical outcome of patients with a posterior chronic anal fissure has been investigated.²³ Fissure healing and symptomatic improvement were achieved in both groups of patients. At two months after injection, 89% of patients in Group 1 (20 units) had a healing scar, while 96% in Group 2 (30 units) had a healing scar; these results confirm that higher doses lead to higher success rate.²³ Resting anal pressures were significantly lower than pretreatment values in both groups; although maximum voluntary pressure was unchanged in patients treated with 20 units, it was significantly lower than pretreatment value in patients treated with 30 units, probably related to a diffu-

TABLE 1. Review of experience using botulinum neurotoxin for the treatment of chronic anal fissure

Reference	Patients (n)	Dose (MU)/drug	Healing rate at 6–8 wk (%)	Temporary incontinence (%)	Recurrence (%)	Complications (%)
Gui et al., 1994 ³¹	10	15 BOTOX	70	10	20	10
Jost and Schimrigk, 1994 ³⁵	12	5 BOTOX	83	0	8	0
Jost and Schimrigk, 1995 ³³	54	5 BOTOX	78	6	6	11
Mason et al., 1996 ³⁶	5	Nr Dysport	60	0	0	0
Jost, 1997 ²⁸	100	5 BOTOX	82	7	6	0
Espi et al., 1997 ³⁷	36	10/15 BOTOX	65/81	0	0	0
Maria et al., 1998 ⁴³	25	20 BOTOX	88	4	0	0
Maria et al., 1998 ⁴³	57	15/20 BOTOX	44/68	0	0	0
Minguez et al., 1999 ²⁶	69	10–21 BOTOX	48–70	0	37–52	0
Jost and Schrank, 1999 ³²	50	20/40 Dysport	76/80	4/12	4/8	0
Brisinda et al., 1999 ²²	25	20 BOTOX	96	0	0	0
Fernandez et al., 1999 ³⁸	76	40 BOTOX	67	3	0	1
Khademi and Feldman, 2000 ^{39a}	11	25 BOTOX	82	0	0	0
Maria et al., 2000 ⁴²	50	20 BOTOX	74	0	0	0
Lysy et al., 2001 ^{40a}	30	20 BOTOX	73	0	0	—
Madalinski et al., 2001 ^{41a}	14	25–50 BOTOX	54	0	8	—
Tilney et al., 2001 ³⁰	10	Nr Dysport	Nr	Nr	Nr	20
Madalinski et al., 2002 ⁴¹	139	25–50–100 BOTOX	Nr	7.8	Nr	6
Brisinda et al., 2002 ⁸	150	20/30 BOTOX	89/96	3	4	0

^aPlus topical nitrates.

Nr, not reported. Dysport is trade name of the type A botulinum toxin preparation manufactured by Ipsen (Maidenhead, UK); BOTOX is the trade name of the type A preparation manufactured by Allergan (Irvine, CA). There has been much confusion over the doses and units of potency of the two preparations; although doses are quoted in mouse units (mu), implying some standardization, BOTOX seems to be more potent. It is suspected that 1 mu BOTOX, is equivalent to 3–5 mu Dysport; a Dysport:BOTOX, equivalency ratio of approximately 3:1 or 4:1 at standard vial dilutions has been suggested.

sion of BoNT to EAS. Five of these patients reported mild incontinence of flatus that lasted 2 weeks after treatment and disappeared spontaneously. BoNT diffusion in the tissues is a dose-dependent phenomenon: histochemical staining of acetylcholinesterase suggested that higher doses produced a biological effect throughout the entire muscle, whereas smaller doses produced a gradient down the length of the muscle studied.

It has been observed that BoNT injections into the striated EAS are also effective for treating fissure. The mechanism is probably mediated by diffusion to the IAS, as shown by the observation that maximum squeeze pressure and resting pressure are both reduced with this procedure. Because the fundamental pathogenic event in chronic fissure is the IAS spasm, the injection into the EAS is not the first choice for treatment. In addition, the IAS is readily visible and easier to inject than the EAS.

Complications of the treatment have been reported by several authors. Reported side effects, other than transitory incontinence for flatus or feces, encompass perianal thrombosis and hematoma.³⁰ However, the development of potential complications does not seem to influence the overall efficacy of the treatment.^{23,28,30–44}

Pelvic Floor Dysfunction: Outlet-Type Constipation and Anterior Rectocele

Constipation is a common primary presenting symptom and one of the most common chronic complaints. A

diagnosis of constipation is made when less than three bowel movements per week and at least one of the following occur on a minimum of 25% of occasions: hard bowel movements, difficulty passing the bowel movement, sense of inadequate defecation. Patients with chronic idiopathic constipation can be classified in two groups: slow transit constipation and pelvic floor dysfunction. This latter category is characterized by a failure of the puborectalis muscle to relax during efforts to defecate, or by its paradoxical contraction. With an effort to evacuate the rectum, the puborectalis and the EAS normally relax to straighten the anorectal angle and open the anal canal.

The etiology of pelvic floor dysfunction is unclear. Prolonged efforts to empty the rectum may aggravate the condition. It has been suggested that paradoxical puborectalis contraction during straining represents a focal dystonia, characterized by excessive recruitment of synergistic and antagonistic muscle groups during voluntary activity and lack of reciprocal inhibition. BoNT has been used to selectively weaken the EAS and puborectalis muscle in constipated patients; as a consequence, the anorectal angle increases during straining, and evacuation becomes possible (Table 2).

Outlet-type constipation may also occur in Parkinson's disease (PD).⁸ Following the observation of the dramatic improvement of a PD patient with outlet-type

TABLE 2. Published results of treatment of outlet type constipation with botulinum neurotoxin

Reference	Patients (n)	Dose (MU)/drug	Results	Complications
Hallan et al., 1988 ¹⁰⁶	7	NR/Dysport	Maximum voluntary contraction from 70 to 28 cmH ₂ O. Anorectal angle from 96 to 124 degrees. Symptomatic improvement in 4 patients.	Incontinence in 2 patients
Joo et al., 1996 ¹⁰⁷	4	6–15/BOTOX	Symptomatic improvement in all treated patients. Two patients relapsed.	0
Shafik et al., 1998 ¹⁰⁸	15	25/BOTOX	Symptomatic improvement in 13 patients, on average 4.8 months after the first treatment.	0
Maria et al., 2000 ¹⁰⁹	10 PD	30/BOTOX (3 patients)	Anal tone during straining from 95 mmHg to 38 mmHg at 8 weeks.	NR
		60/BOTOX (1 patient)	Increment of anorectal angle.	
		100/BOTOX (6 patients)		
Maria et al., 2000 ²⁹	4	30/BOTOX	75% were improved at 8 weeks. Anal tone during straining from 96.2 mmHg to 42.5 mmHg at 4 weeks, and to 63.2 mmHg at 8 weeks. Anorectal angle from 94° to 114°.	0
Maria et al., 2000 ²⁹	14 AR	30/BOTOX	Symptomatic improvement in 9 patients.	0
Ron et al., 2001 ¹¹⁰	25	20/BOTOX	Symptomatic improvement in 75% of the patients.	Perineal pain in 3 patients
Madalinski et al., 2002 ⁴¹	39	25/BOTOX	NR	Perineal pain in 4 patients
		150/Dysport		

Nr, not reported. Dysport is trade name of the type A botulinum toxin preparation manufactured by Ipsen (Maidenhead, UK); BOTOX is the trade name of the type A preparation manufactured by Allergan (Irvine, CA, USA).

NR, ???; PD, Parkinson's disease; AR, anterior rectocele.

constipation treated with BoNT injections into the puborectalis muscle, we performed a prospective study to identify the prevalence of this condition among PD outpatients. Patients with a diagnosis of PD filled out an inventory of gastrointestinal function (evaluating the number of bowel movements and defecatory function) and received a proctological evaluation. A total of 138 patients met the inclusion criteria for chronic constipation; 18 of them (13%) had isolated or prominent outlet-type constipation. Ten patients, treated with levodopa, dopamine agonists, and domperidone, were studied. One-hundred BoNT units were injected in the puborectalis muscle under transrectal ultrasonography guidance. After treatment, anal tone during straining was reduced from 97.4 ± 19.6 mm Hg at baseline to 38.2 ± 10.4 mm Hg 2 months after treatment ($P = 0.00001$), and anorectal angle during straining (as measured with defecography) increased from a mean of 99 degrees ± 7.9 before treatment to 122.2 degrees ± 15 ($P = 0.0004$).

Rectocele is a hernia of the anterior rectal wall into the lumen of the vagina. If less than 2 cm in diameter, rectocele is considered a normal finding in constipated or healthy subjects. When the diameter increases beyond 2 cm, the rectocele can cause outlet obstruction and rectal emptying difficulties.^{45,46} It has been suggested that, in some instances, the rectocele is caused by failure of relaxation or paradoxical contraction of the puborectalis muscle occurring during attempted evacuation, but the reason for its establishment is not clear. It is conceivable

that straining enlarges the rectocele and makes evacuation even more difficult.

A wide variety of surgical approaches have been proposed with the aim of ensuring rectal emptying by reducing the dimension of the rectocele. However, surgical results are often disappointing; repair, either vaginal, transperineal, or transanal, does not always alleviate symptoms, and in some patients causes impaired fecal continence. Recently, 14 women were treated with a total of 30 BoNT units.⁴⁵ At 2-month evaluation, a symptomatic improvement was found in 9 patients. At same time, the rectocele depth was reduced from 4.3 ± 0.6 cm to 1.8 ± 0.5 cm ($P < 0.001$) and the rectocele area was reduced from 9.2 ± 1.3 cm² to 2.8 ± 1.6 cm² ($P < 0.001$), while the anorectal angle during straining increased from 98 ± 15 degrees to 121 ± 19 degrees ($P = 0.001$).⁴⁵

Chronic Idiopathic Anal Pain

Chronic idiopathic anal pain is part of a rather ill-defined group of disorders termed chronic idiopathic perineal pain, which also includes proctalgia fugax and coccygodynia.^{47,48} The main feature of these syndromes is that no objective abnormalities are found on clinical examination, and the distinction between the different groups of perineal pain is based solely on the patient's description of the pain and location of tenderness by palpation. In the majority of patients, the pain is present constantly, usually intense, sometimes burning, often

with some irradiation; it was usually aggravated by sitting, whereas defecation had no constant effect, and is relieved by lying down. The pathogenesis of the syndrome are unknown. There is no satisfactory treatment for chronic anal pain⁴⁹; nonetheless, anal stretch and LIS are still used in several patients on the assumption that the pain might be caused by a hypertonic IAS, because no objective changes can be demonstrated. Recently, injections of BoNT (20 units placed intersphincterically in four quadrants and/or at the lower rim of the puborectalis muscle under ultrasonographic guidance) resulted in improvement in 4 patients with chronic anal pain that persisted during a follow-up of 12 to 24 months.⁵⁰

APPLICATIONS IN THE UPPER GIT

Recently, interest has focused on the use of BoNT to treat motility disorders of the upper GIT. BoNT may have a potential for treating these motility disorders, which are debilitating, considering that surgery may be judged too invasive and pneumatic dilation too risky.

Achalasia

Achalasia is a failure to relax the LES that remains tonically contracted, resulting in a functional esophageal obstruction.^{5,6} The cause may be a generalized loss of enteric neurons or a selective loss of the inhibitory VIP- and NO-containing neurons located in esophageal myenteric plexus. NO synthase is undetectable in the myenteric plexus and in the nerve fibers reaching the esophagus and the cardias.^{6,51} Esophageal ganglion cells and neurons of the dorsal motor nucleus of the vagus are decreased in number, and the vagus nerves degenerate. NO-containing neurons are primarily involved, while cholinergic neurons may be spared.^{52,53} The preserved cholinergic innervation to LES induces increased sphincter pressure that is a characteristic feature of this disorder. It has been postulated that an autoimmune reaction against a dopamine carrier protein located in the myenteric plexus may cause achalasia.⁵⁴ Some diseases may cause ENS dysfunction resulting in secondary achalasia; they include paraneoplastic syndromes, Chagas' disease, and PD. Familial achalasia occurs in several genetic disorders, and clinical severity may vary among family members.

The degenerative neural lesions of achalasia cannot be corrected by the treatment, which is therefore symptomatic. Classic therapies were aimed to mechanically reduce LES tone by means of drug therapy, pneumatic dilation, or surgical myotomy. These procedures are efficacious in the majority of patients (65–90%) but carry a significant risk of complications.^{6,55} Perforation occurs

in 2 to 5% of patients, and gastroesophageal reflux is reported by 10 to 50% of patients after myotomy. In addition, repeated procedures are sometimes required after dilation.

Results of BoNT Treatment.

The limitations of classic procedures prompted the use of injections of BoNT into the LES, based on the rationale that BoNT injections would inhibit an unbalanced cholinergic influence on the sphincter and improve esophageal emptying.^{56–81} The LES is easily injected during an upper endoscopy using a 5-mm sclerotherapy needle. Endoscopic ultrasonography has been used to guide injections, in an effort to maximize the amount of BoNT delivered to LES.

Short-term symptomatic relief occurs in 70 to 100% of patients (Table 3).^{56–58,63,64,82–85} The occurrence of vigorous achalasia has been described as the principal determinant of the response to BoNT.^{62,86,87} LES pressure decreases and esophageal emptying improves in parallel to symptomatic relief but to a lesser degree than after dilation. Other drawbacks of the treatment with BoNT have been observed recently. Classic surgical procedures and BoNT treatment have equal success rates, but in the long-term, the efficacy of BoNT is significantly shorter than that of dilation. BoNT is more expensive than pneumatic dilation, particularly due to the need of repeated treatments. Another limitation of BoNT treatment is the lack of an initial symptomatic response and a high residual LES pressure (≥ 18 mm Hg). Nevertheless, there are obvious advantages of BoNT treatment: the procedure is endoscopic, long-term efficacy is reasonable, and the treatment is safe in older patients with tortuous megaesophagus or epiphrenic diverticulum,⁸¹ in whom dilation is highly risky. It has been noted recently that BoNT is also efficacious on pediatric patients suffering from achalasia.^{88,89} For this reason, it has been recommended that BoNT be used only for children with achalasia who are poor candidates for dilation or myotomy.

Other Esophageal Disorders

Cricopharyngeal dysphagia derives from a dysfunction of the cricopharyngeal muscle (upper esophageal sphincter, UES),⁵ which can be primary or secondary to several conditions, such as cerebrovascular accidents, amyotrophic lateral sclerosis, and lesions of the skull base. Proximal dysphagia is the typical clinical presentation and pharyngeal diverticula are possible aftermaths. Increased UES function has been traditionally treated with myotomy, dilatation, or neurectomy of the oropharyngeal plexus. Localized BoNT injections have also been successfully used.^{90,91} The best

TABLE 3. Review of experience using botulinum neurotoxin for the treatment of achalasia

Reference	Description	Patients (n)	Results/conclusions
Pasricha et al., 1995 ⁶⁴	BoNT vs. Placebo	21	67% were improved at 6 weeks.
Annese et al., 1996 ⁶⁶	BoNT vs. Placebo vs. PBD	16	100% were improved at 1 month. 88% required repeated injections. BoNT is as effective as pneumatic dilation.
Fiorini et al., 1996 ⁶⁶	BoNT vs. placebo	13	72% were improved at 3 months.
Pasricha et al., 1996 ⁶³	BoNT	31	60% (82% of those aged >50) were improved at 3 months.
Fishman et al., 1996 ⁶⁷	BoNT	65	60 idiopathic cases: BoNT treatment improved symptoms of dysphagia, chest pain and regurgitation in the majority of patients. 5 secondary cases: there was no response to BoNT in 4 patients. Patients, who respond to a first BoNT injection, but relapse, may respond to a second treatment.
Cuilliere et al., 1997 ⁶⁸	BoNT	55	60% were improved at 6 months.
Brant et al., 1999 ⁶⁹	BoNT in Chagas' disease	3	Clinical improvement occurred in all patients. Mean LES pressure dropped by 29%.
Kolbasnik et al., 1999 ⁷⁷	BoNT	30	Symptomatic improvement for >3 months was seen in 77% of patient. 7 patients had a sustained response after a single injection; 16 relapsed and required re-treatment.
Annese et al., 1999 ⁵⁷	Botox vs. Dysport	78	Type A BoNT have comparable efficacy in esophageal achalasia after up to 6 months after treatment.
Muehldorfer et al., 1999 ⁷⁸	BoNT vs. PBD	24	The two treatments had equal initial success rate (dilation 83%, BoNT 75%). In the long-term the efficacy of BoNT injection was statistically significantly and shorter than that of balloon dilation.
Panaccione et al., 1999 ⁷⁹	BoNT vs. PBD	NR	Intrasphincteric BoNT injection was more costly pneumatic dilation (USD 5,033 compared to USD 3,608). BoNT treatment may be less costly if life expectancy is less than 2 years.
Greaves et al., 1999 ⁸⁰	BoNT	11	The relapse rate was 73% within 2 years from treatment. There were a beneficial effect on dysphagia, no improvement in chest pain or regurgitation scores, and no reduction of mean LES pressure.
Wehrmann et al., 1999 ⁸¹	BoNT in high risk patients	20	80% were improved at 6 weeks. Mean cardia diameter was increased from 2.1 mm to 3.2 mm. The patients who initially had a symptomatic relapse after an average of 5 months. BoNT re-injections were efficacious.
Hurwitz et al., 2000 ¹¹¹	BoNT in children	23	The mean duration of effect in 19 responders was 4.2 months. 50% of the patients required an additional procedure (pneumatic dilation, surgery) on average 7 months after the first treatment.
Annese et al., 2000 ⁵⁶	BoNT dose rasing study	118	82% of the patients were responders at 1 month. No dose related effect was observed. Vigorous achalasia was the main determinant of the response to BoNT.
Ip et al., 2000 ⁷⁶	BoNT in children	7	100% were improved at 4 months. Sustained response beyond 6 months occurred in 43% of patients.
Hep et al., 2000 ⁷⁵	BoNT plus PBD	3	Propulsive peristalsis of the esophagus was restored in all patients.
Mikaeli et al., 2001 ⁷⁴	BoNT vs PBD	40	Cumulative 12-month remission rate was significantly higher after a single pneumatic dilation (53%) compared to a single BoNT injection (15%, $P < 0.01$). The 12-month estimated adjusted hazard for relapse and need for retreatment for BoNT group was 2.69 times that of the pneumatic dilation group.
Allescher et al., 2001 ⁷³	BoNT vs PBD	37	After 24 months, a single pneumatic dilation was superior to a single BoNT injection, and after 48 months all patients treated by BoNT injection had experienced a symptomatic relapse.
Ghoshal et al., 2001 ⁷²	BoNT vs PBD	17	Both therapies resulted in a significant reduction in LES pressure.
Zarate et al., 2002 ⁷¹	BoNT	17	The effect of BoNT injection wanes with time in elderly patients, necessitating repeated injections to keep the patients symptom-free.
D'Onofrio et al., 2002 ⁷⁰	BoNT	37	Of the 35 patients followed, 12 had a relapse and were retreated; 4 of 12 did not respond after retreatment. One or two injections of BoNT result in a clinical and objective improvement in about 84% of achalasia patients and are not associated with serious side effects; patients over 50 years of age showed better benefit than younger patients.

BoNT, botulinum toxin; LES, lower esophageal sphincter; PBD, pneumatic balloon dilation. Dysport is trade name of the type A botulinum toxin preparation manufactured by Ipsen (Maidenhead, UK); BOTOX is the trade name of the type A preparation manufactured by Allergan (Irvine, CA).

results were obtained in pure cricopharyngeal spasm and pharyngeal diverticula.

A simplified percutaneous technique with electromyographic guidance has also been developed to inject the

UES.⁹²⁻⁹⁴ The muscle is reached after manual rotation of the larynx by inserting an electromyography recording needle through the skin and advancing it behind the thyroid lamina until muscle motor unit potentials are recorded.

Diffuse esophageal spasm is a poorly understood disorder, where patients experience chest pain or dysphagia as a result of repetitive and simultaneous high-amplitude esophageal contractions. A small series of patients with manometrically proven diffuse spasm has been treated with BoNT injections into the LES. Two months after treatment, 80% of patients had scored a 50% or greater decrease in a scale for dysphagia and chest pain.

Isolated hypertensive LES is characterized by high LES pressure and normal peristalsis. The mechanism of dysphagia remains unclear, but incomplete LES relaxation may play a role in several patients. Dilation has been used with good results in the patients with significant dysphagia who failed conservative therapy. Recent attention has focused on endoscopic injection of BoNT directly into the LES. Short-term responses have been favorable without any significant complication after treatment with 80 BoNT units.

Gastropyloric Disorders

BoNT injection into the gastric antrum may be used to transiently decrease gastric emptying as a treatment for obesity. Preliminary data in rats have shown a significant loss of body weight associated with a reduction of dietary intake in the BoNT-treated group.⁹⁵

BoNT has been used to facilitate gastric emptying in patients who underwent pylorus-preserving duodenopancreatectomy,⁹⁶ and, recently, to treat idiopathic gastroparesis.^{97–99} Antral hypomotility is thought to be a major factor in this condition, and increased gastric outlet resistance due to pyloric dysfunction has been described in gastroparesis, primarily the diabetic kind. Initial studies suggests that BoNT injection into the pylorus improves both gastric emptying and symptoms.

Infantile hypertrophic pyloric stenosis is a congenital hereditary disorder characterized by a functional gastric outlet obstruction. Obstruction is the result of a gradual hypertrophy of the circular smooth muscle of the pylorus, and the neurons that innervate the circular-muscle layer lack NO synthase. Recently, lack of response to BoNT injection in 2 patients with pyloric stenosis has been observed.¹⁰⁰

Sphincter of Oddi Dysfunction

Recurrent upper abdominal pain is a common clinical problem affecting 10% or more patients undergoing cholecystectomy. Sphincter of Oddi dysfunction has been implicated in the etiology of 10 to 20% of these cases. Experimental studies have demonstrated that local injections of BoNT significantly reduce wave amplitude and phasic contractile activity in the sphincter of Oddi, by means of a selective inhibition of cholinergic influenc-

es.^{101,102} At least two potential uses of BoNT can be hypothesized: first, an intrasphincteric injection may serve as a handy test to select patients whose pain is directly related to Oddi dysfunction; second, repeated BoNT treatments may provide a treatment modality alternative to sphincterotomy.^{103–105}

Recently, 15 consecutive patients with frequent attacks of acute pancreatitis and manometrically proven sphincter of Oddi dysfunction have been treated by endoscopy with 100 BoNT units into the major papilla. Twelve patients have remained asymptomatic for 3 months after treatment. Of the 12 patients, 11, who initially responded, had a symptomatic relapse on average 6 months after BoNT treatment.¹⁰⁴

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