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Review article: the use of botulinum toxin in the alimentary tract

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SUMMARY

New and future indications for the treatment of disorders of the alimentary tract using local injections of botulinum toxin are reviewed. Clinical experience shows that overactive smooth muscle sphincters may be weakened to treat disorders such as achalasia or chronic anal fissure. By contrast, injections placed into the sphincter of Oddi have proven less effective for post-cholecystectomy pain syndrome. Experimental evidence suggests that food intake may be reduced by weakening the distal stomach with botulinum toxin. This approach may possibly lead to the treatment of obesity. There are some new possible indications for the use of botulinum toxin on the alimentary tract, and infantile hypertrophic pyloric stenosis seems to be the most promising new development.

INTRODUCTION

Gastrointestinal and neurological symptoms are the main features of human botulism. Today, this disease is rare and takes up only few pages in textbooks. Different serotypes of *Clostridium botulinum* produce a slightly different spectrum of clinical signs and symptoms (Table 1). While a number of clinical features are related to weakness of the striated muscles, others such as a dry mouth or blurred vision, constipation, diarrhoea, nausea, vomiting or abdominal cramps are associated with the action of the toxin on the autonomic nervous system. From observations such as these came the hypothesis that botulinum toxin (BTX) may act on cholinergic autonomic nerve terminals, as well as on cholinergic terminals innervating the skeletal muscles.

Experiments *in vitro*, however, showed that BTX could inhibit not only the postganglionic cholinergic neurones supplying the longitudinal smooth muscle of the guinea-pig ileum, but also the noradrenergic motor response of the rat anococcygeus muscle and the neurogenic excitatory response of the guinea-pig bladder.[1] Interestingly, no effect was observed on the non-adrenergic inhibitory response of the guinea-pig fundic strip and taenia coli,[1,2] suggesting that BTX may be specific for excitatory autonomic innervation. It is now clear that the different serotypes of botulinum toxin inhibit neurotransmitter release by cleaving different synaptic proteins after having been internalised.[3–5] Botulinum neurotoxins are specific for components of the neuroexocytosis apparatus; thus, the only limiting factor for BTX is the presence of specific acceptors on the presynaptic membrane (Figure 1). Once it has been internalised, BTX is not specific for cholinergic transmission.[6]

There is already evidence in the literature about the use of BTX to modify gastrointestinal motility.[7–11] In most of these studies the toxin has been used to reduce the power of contraction of smooth muscles; in a minority of cases it has been injected into striated muscles.

THE ALIMENTARY TRACT

Movement involving the alimentary tract is an interesting topic, because alimentary function depends entirely on gastrointestinal motility. Although the alimentary tract is a tube, it does not have the basic properties of a tube, as without motion there is no propulsion. Everything in the gastrointestinal tract

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Table 1. Symptoms and signs in patients with the common type of human botulism[20]

	Type A (%)	Type B (%)	Type C (%)
Neurological symptoms			
Dysphagia	96	97	82
Dry mouth	83	100	93
Diplopia	90	92	39
Dysarthria	100	69	50
Upper extremity weakness	86	64	NA
Lower extremity weakness	76	64	NA
Blurred vision	100	42	91
Dyspnea	91	34	88
Paresthesiae	20	12	NA
Gastrointestinal symptoms			
Constipation	73	73	52
Nausea	73	57	84
Vomiting	70	50	96
Abdominal cramps	33	46	NA
Diarrhoea	35	8	39
Miscellaneous symptoms			
Fatigue	92	69	84
Sore throat	75	39	38
Dizziness	86	30	63
Neurological findings			
Ptosis	96	55	46
Diminished gag reflex	81	54	NA
Ophthalmoparesis	87	46	NA
Facial paresis	84	48	NA
Tongue weakness	91	31	66
Pupils fixed or dilated	33	56	75
Nystagmus	44	4	NA
Upper extremity weakness	91	62	NA
Lower extremity weakness	82	59	NA
Ataxia	24	13	NA
DTRs diminished or absent	54	29	NA
DTRs hyperactive	12	0	NA
Initial mental status			
Alert	88	93	27
Lethargic	4	4	73
Obtunded	8	4	0

DTRs: deep tendon reflexes.
NA: not available.

depends on its ability to move. Two main antagonistic forces are involved: one is propulsion (i.e. gastrointestinal motility) and the other is retention by specialized sphincters, which is also brought about by active contraction. The details of the basic patterns of motility are summarized in Table 2.

The most important organized contraction of the alimentary tract is the migrating motor complex. The

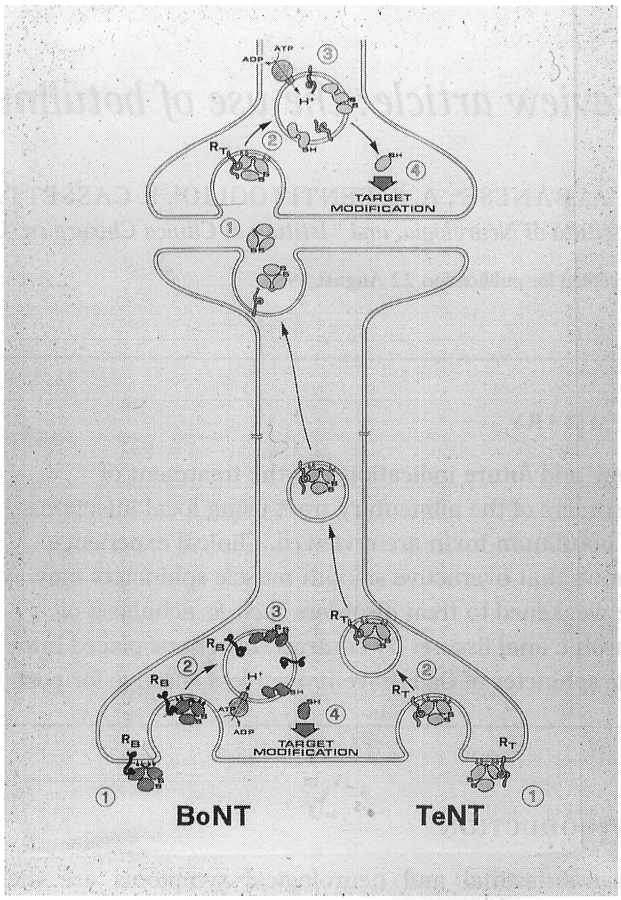

Figure 1. Mechanism of action of botulinum (blue) and tetanus (yellow) neurotoxins. 1. The toxin binds to a specific acceptor outside the presynaptic membrane. 2. Then the toxin is internalised by active endocytosis and is accumulated into endoplasmic vesicles. At variance with tetanus toxin, botulinum toxins are released in the same terminal where they have been first internalised. 4. After release, the toxin modifies its specific target and inhibits neurotransmitter release. (By courtesy of G. Schiavo.)

oesophagus has primary, secondary and tertiary waves, while the stomach exhibits two distinct contractions: fundic relaxation accommodates food, but antral peristalsis shears food and delivers solids to the small intestine. Giant migrating complexes become more important for propelling food through the intestines as one descends toward the colon.

OESOPHAGUS

Some of the earliest reports on the use of BTX have involved the oesophagus[7] for the treatment of achalasia. Less common motility disorders, such as nutcracker

Table 2. Organized contractions of the alimentary tract interact to control motility at different levels[12]. Control of propulsion by smooth muscle sphincters is not reported here

Site	Contraction	Proposed purpose	Inter-digestive frequency
Oesophagus	Primary wave	Deliver food to stomach	Quiet
	Secondary wave	Housekeeping of oesophagus	Irregular
	Tertiary wave	Housekeeping of oesophagus	Irregular
Stomach	Fundic tone	Accommodate food, deliver liquid to duodenum	Constant
	Antral peristalsis (MMC)	Shearing of food, delivery of solids to duodenum	Every 100 min
Small bowel	Individual phasic contraction	Basic unit of contraction	2 per h
	MMC	Inter-digestive housekeeper	Every 100 min
	Migrating cluster contraction	Inter-digestive housekeeper	Every 100 min
		Postprandial propulsion	5–10 per h
	Giant migrating contraction	Strongest contraction; housekeeping of distal small bowel	Irregular
	Retrograde giant contraction	Mixing of intraluminal contents	
Colon	Phasic contraction	Mixing of intraluminal contents	
	Short duration		2–13 per min
	Long duration		0.5–2 per min
	Organized contraction	Slow anterograde and retrograde propulsion	1 every 35–50 min (dog)
	Propagating, MMC		
	Non-propagating, MMC-like		
	Giant migrating contraction	Rapid anterograde propulsion	2–4 every 24 h

MMC: migrating motor complex.

oesophagus, and diffuse oesophageal spasm, have not been treated with botulinum toxin.

Recently, a double-blind study has confirmed the efficacy of BTX for the treatment of achalasia.[8] Eighty units Botox (Allergan, Irvine, CA) or placebo were injected endoscopically into the lower oesophageal sphincter. Clinical improvement was observed very early in the BTX-treated group. One week after treatment, pressure in the lower oesophageal sphincter was reduced by an average of 33% and oesophageal retention was reduced by 35%. More than half of the patients treated with BTX were still in remission 6 months after a single treatment.

STOMACH

The stomach consists of three functionally independent sections.[12] The proximal stomach stores chyme and propels it towards the antrum; the distal stomach mixes and grinds chyme, and propels it distally; the pylorus controls emptying and prevents reflux. The functional division into three different sections explains the different effects of various types of surgical interventions on the vagus nerve. Proximal gastric vagotomy impairs receptive relaxation and accommodation in the proximal stomach, while allowing normal antral contractions and normal gastric emptying of solids. Total gastric vagotomy and truncal vagotomy impair receptive relaxation and accommodation in the proximal stomach and it allows rapid gastric emptying of liquids; in the distal stomach there are weakened antral contractions and delayed gastric emptying.[13] Surgical truncal vagotomy requires pyloroplasty or gastroenteric anastomosis in order to assure gastric emptying.

We attempted to reduce the body weight of rats by reducing the rate of gastric emptying [unpublished observation]. We injected BTX-A into the distal part of the stomach, which is responsible for propelling food towards the small intestine. First, we constructed a dose–response curve which showed that 20 units of Botox distributed over six sites in the distal stomach of the rat produced a reduction in body weight lasting for approximately 1 month. This prompted us to set up a controlled study that is still in progress. The preliminary results are presented here.

Two groups of Wistar rats aged 6 months, with a stable weight curve (average 600 g) were studied. Group A rats ($n = 5$) were treated with 20 units Botox (4 mL distributed over six sites) in the gastric antrum; group B rats ($n = 4$) were injected with the same amount of saline. All the animals lost weight after surgery. Group B rats started to regain weight about 2 weeks later, while group A animals continued to lose weight for about 1 month, then gradually regained it. During the period of weight

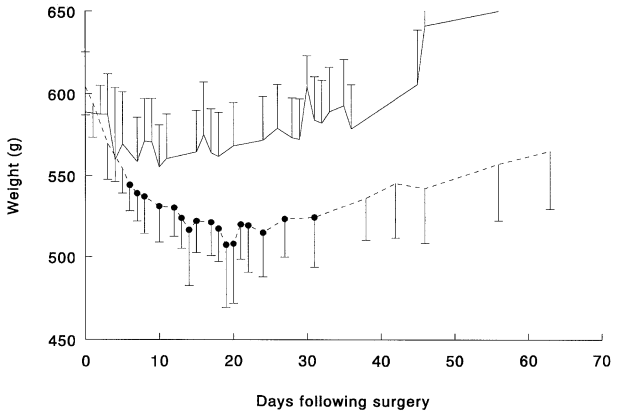

Figure 2. Weights measured in two groups of rats following the injection of 20 units of Botox (dashed line) or of saline (solid line) in the distal stomach. Filled circles in the lower plot indicate differences between the two groups that are statistically significant ($P < 0.01$).

loss, group B rats ingested smaller quantities of food than group A. A between-group comparison of their weights showed statistically significant differences during the period from days 8 to 31 following surgery (Figure 2). This demonstrated that food intake can be reduced by preventing the stomach emptying into the intestines.

SPHINCTER OF ODDI

Patients with post-cholecystectomy pain syndrome, who were diagnosed with sphincter of Oddi dysfunction, received BTX injections by a sclerotherapy needle passed through a duodenoscope.[9] In both patients, bile flow or sphincter pressure improved, but neither patients had any appreciable improvement in pain. Both eventually had endoscopic sphincterotomy.

ANORECTAL MOTILITY

Anorectal motor control involves the pelvic floor muscles and two sphincters, one striated and one smooth. Normally, the smooth internal sphincter provides about 80% of resting anal pressure, while the striated external sphincter contributes to voluntary straining pressure. Either pressure can easily be measured in the clinic by anal manometry. The contraction of the pelvic floor and striated anal sphincter causes closure of the pelvic floor outlet. There are two main theories to explain continence, the flutter valve theory and the three-sling theory.

The flutter valve theory postulates that contraction of the puborectalis muscle pulls the posterior rectal wall anteriorly, making the anorectal angle more acute. The anal canal closes as the anterior rectal wall comes into contact with the posterior rectal wall over the puborectalis and anorectal ring. In the three-sling theory, the superficial sphincter pulls the anal canal anteriorly towards the perineal body, the deep external sphincter contracts to pull the anal canal posteriorly towards the coccyx, and the puborectalis muscle draws the anal canal anteriorly. The muscular slings contract in opposite directions to close the anal canal. There is no clear evidence yet favouring one over the other, and the true source of faecal continence is probably a combination of these two postulated mechanisms.[14] Anismus, which is a severe form of constipation, has been treated with local injections of BTX into striated muscles of the pelvic floor.[11,15]

An idiopathic anal fissure is a tear of the anoderm in the antero-posterior mid-line, which will become an ulcer over time. Anal fissure may be acute or chronic. Nearly 50% to 70% of acute fissures will resolve spontaneously, while chronic fissure usually will not.[14] Chronic anal fissures are usually located posteriorly. This location has been related to a concomitant reduction of blood flow into the posterior anal artery due to the chronic contraction. We have been interested in chronic anal fissure because the pathophysiology of this common condition is based on a vicious circle involving pain and increased resting pressure, which depends on a contraction of the smooth sphincter (Figure 3).

We have published a pilot study on the use of BTX to treat chronic anal fissure in 10 patients.[16] The number of

Table 3. Time-course of signs and symptoms following treatment of chronic anal fissure with BTX

Clinical features	1 week		1 month		2 months	
	Reduction	Disappearance	Reduction	Disappearance	Reduction	Disappearance
Post-defecatory pain	8	8	3	11	2	14
Pain during exploration	8	7	3	11	3	12
Inspection (healing scar)	0	11	14			

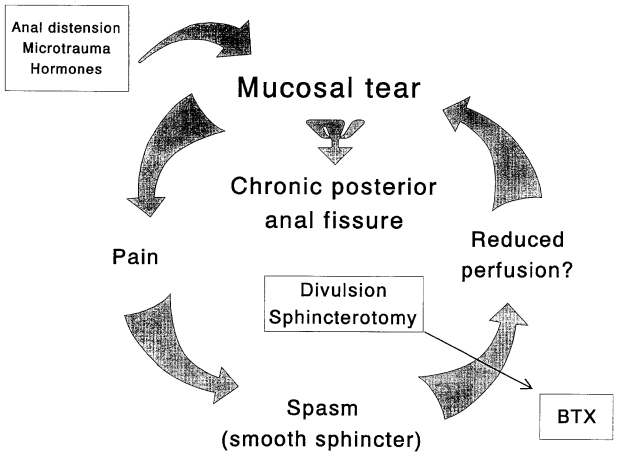

Figure 3. Chronic posterior anal fissure is sustained by a vicious circle involving pain, which brings about a local spasm. The spasm is believed to reduce perfusion through the posterior anal artery, which in turn does not allow the mucosal tear to heal. Surgical interventions (e.g. divulsion, sphincterotomy) permanently reduce muscle strength and the effects of the local spasm. BTX acts with a similar mechanism but its effects are not permanent.

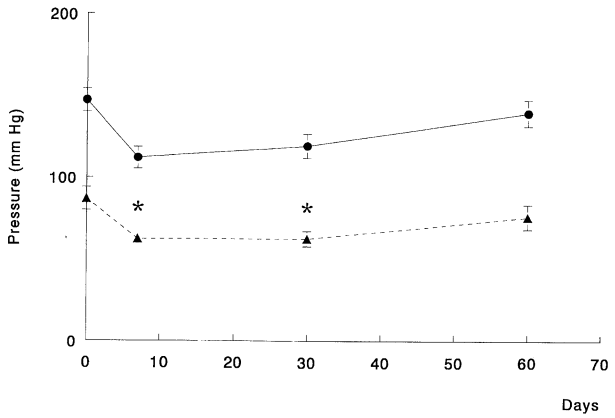

Figure 4. Variation of resting pressure (triangles) and of maximum voluntary pressure (circles) following injection of BTX-A into the internal anal sphincter in patients affected by chronic posterior anal fissure. Asterisks indicate values that are significantly different from day 0 ($P < 0.01$).

patients under study has now increased to 17 (nine females and eight males). Patients had a mean age of 45.6 ± 4.4 years and a mean disease duration of 11.4 ± 2.4 months, indicating that their fissure was chronic. Patients were treated with 15 units of Botox, injected into the internal smooth sphincter, and were followed-up for a period of 2 months. In 14/17 patients a healing scar was observed after 2 months. Two of these patients then had a relapse, one of whom was re-treated successfully while the other requested surgery. Another patient with a fissure at 2 months was re-treated, with subsequent healing of the fissure. A further patient had a healing scar 1 month after treatment but suffered a relapse which did not respond to further treatment.

Figure 4 shows the pressure results. The resting pressure is a direct function of the internal sphincter while the maximum voluntary pressure is a direct function of the external striated sphincter. It can be seen that at days 7 and 30 there is a statistically significant difference compared with day 0 baseline values. This means that a reduction in the strength of the internal sphincter has occurred, while the strength of the external sphincter and the pelvic floor remained unchanged. This is an interesting observation in so far as this is the first indication of a pathogenic rather than a purely symptomatic indication for BTX. Interestingly, the time of action of the toxin roughly corresponds with the time required to interrupt the vicious circle that maintains the chronic fissure, allowing for spontaneous recovery. Similar results have been obtained by injecting botulinum toxin into the external (striated) sphincter, from which it diffuses to the internal (smooth) anal sphincter.[17]

These data prompted us to begin a double-blind study of chronic anal fissure which is now in progress. We intend to recruit 20 patients. They will be treated starting with 20 units of Botox and will be evaluated 1 week, 1 month and 2 months following the treatment. At monthly evaluations the surgeon may decide to perform a re-treatment. In this case, the patient treated with saline will receive 20 units of Botox, the patients treated with the toxin will receive 25 units.

NEW INDICATIONS

Summing-up, a few speculations on possible new indications for BTX can be drawn.

It may be possible to treat obesity with BTX-A. Clearly 2 or 3 months is a reasonable time for the toxin to reduce the motility in the gastric antrum; therefore, this must be considered a possible indication for non-severe obesity. Probably, long-term treatment of severe obesity may still require surgery; in such cases, however, BTX may be used to control weight before surgery and reduce the operative risk.

It may be possible to produce a targeted paralysis of the intestines. This would be required in selected cases when it is desirable to produce local paralysis and reduce propulsion.

It may be possible to use BTX as a test drug for gastrointestinal motility. There are occasions when the functional ability of the gastrointestinal tract needs to be tested, and this could possibly be achieved using a standardized test dose of BTX.

Finally, we believe that local BTX injections could be used to treat infantile hypertrophic pyloric stenosis, which is one of the most common conditions requiring surgical intervention within the first few months of life.[18] In our opinion, clinical trials should be started as soon as possible in this disease.

The possibility of developing new indications is based on the susceptibility of putative target sites to BTX. There are very few studies available on the distribution of acceptor sites outside the neuromuscular junction. Localization studies failed to demonstrate a binding of ^{125}I-BTX to adrenergic nerve terminals[3]. Black & Dolly[19] observed the labelling of ^{125}I-BTX to putatively cholinergic nerve endings in the mouse ileum, but could not draw definitive conclusions on the chemical nature of the labelled terminals. Even though there are many difficulties in these histochemical studies, it seems clear that the distribution of BTX acceptors in the autonomic nervous system is not haphazard. We therefore foresee the need for a renewed effort aimed at mapping the affinity of different BTX serotypes for autonomic nerve terminals located along the length of the alimentary tract.

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