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The use of Botulinum toxin on smooth muscles

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Smooth muscles of the alimentary tract control gastrointestinal motility. This paper reviews possible ways in which Botulinum toxin A might be used to treat motility disorders. Preliminary results from a controlled study in rats suggest that BOTOX® injected into the distal stomach produces a reduction in body weight through delayed emptying of the stomach. This finding may be relevant to the short term management of obesity. Injection of BOTOX® into the internal smooth sphincter has produced healing scars within 2 months for 14/17 patients with chronic anal fissures. In this way the vicious circle that maintains chronic fissure might be broken, allowing for spontaneous recovery.

Keywords: Alimentary tract – Anal fissure – Botulinum toxin – Botulism – Obesity – Pyloric stenosis

INTRODUCTION

Today, in textbooks on infectious diseases, discussion of botulism covers only a few pages. Table I summarizes the general findings in human botulism taken from the latest edition of 'Principles and Practice of Infectious Diseases' (Bleck, 1995). While a number of these signs and symptoms are related to weakness of the striated muscles, others such as dry mouth or blurred vision, constipation, diarrhoea, nausea, vomiting and 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 A (BTX-A) acts mainly on cholinergic autonomic nerve terminals.

This hypothesis had the merit of focusing interest on the autonomic nervous system. However, the action of BTX-A is not restricted to a specific neurotransmitter, but is related to uptake by nerve terminals. Thus the only limiting factor for BTX-A is the presence of specific receptors on the presynaptic membrane. BTX-A may act on cholinergic as well as on non-cholinergic terminals. There is already some evidence in the literature concerning the use of BTX-A to modify gastrointestinal motility and genito-urinary activity (Dykstra *et al.*, 1988; Tim and Massey, 1992; Pasricha *et al.*, 1993, 1994, 1995). In most of these studies the toxin was used to reduce the power of contraction of smooth muscles; in a minority of cases it was 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, because without motion there is no propulsion. Two main antagonistic forces are involved: one is propulsion (i.e. gastrointestinal motility) and the other is retention by specialized sphincters, brought about by active contraction. Details of the basic patterns of motility are summarized in Table II.

Organized contractions, also called migrating motor complex, are the most important component of gastrointestinal motility. The oesophagus has a primary wave, as well as secondary and tertiary waves, while the stomach exhibits two distinct contractions: fundic activity accommodates food, and antral peristalsis shears food and delivers solids to the small intestine. Giant migrating complexes become more important for propelling food through the intestines as it descends toward the colon.

Oesophagus

Some of the earliest reports on the use of BTX-A have involved the oesophagus (Pasricha *et al.*, 1995) for the treatment of achalasia. Less common motility disorders, such as nutcracker oesophagus (the main cause on non-cardiac chest pain), diffuse oesophageal spasm, non-specific motility disorders, have not been treated with Botulinum toxin.

Stomach

The stomach consists of three functionally independent sections (Zenilman, 1993). The proximal stomach stores

TABLE I. Symptoms and signs in patients with the common types of human botulism (Bleck, 1995)

	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	56
Diminished gag reflex	81	54	NA
Opthalmoparesis	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

Abbreviations: DTRs, deep tendon reflexes; NA, not available.

chyme and propels it toward the antrum; the distal stomach mixes and grinds chyme, and propels it distally; the pylorus controls emptying and prevents reflux.

In the treatment of obesity, reducing the absorption of food in the bowels can contribute to a reduction in weight; this can be achieved through surgical vagotomy to delay gastric emptying. We investigated the possibility that injection of BTX-A into the distal part of the stomach of rats might reduce intestinal absorption by reducing gastric emptying.

Initially, we constructed a dose–response curve which showed that 20 units BOTOX® distributed over six sites in the distal stomach of the rat produced a reduction in body weight lasting for approximately one month. This prompted a controlled study which 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) injected at time of surgery into 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 one month, then gradually regained it. During the time of weight loss, group A rats ingested lower amounts of food than group B rats. Between-group comparison of weight showed statistically significant differences during the period from days 8 to 31 following surgery (Fig. 1). This demonstrated that intestinal absorption can be reduced by preventing the stomach emptying into the bowels.

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.

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 (Fleshman, 1993). Anismus, which is a severe form of constipation, has been treated with local injections of BTX-A into striated muscles of the pelvic floor (Hallan *et al.*, 1988; Tim and Massey, 1992).

An idiopathic anal fissure is a tear of the anoderm in the anteroposterior mid-line, which will become an ulcer over time. Anal fissure may be acute or chronic. Nearly 50–70% of acute fissures will resolve spontaneously, while chronic fissures generally do not (Fleshman, 1993). 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 (Fig. 2)

TABLE II. Basic patterns of motility in the alimentary tract

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 hr
	MMC	Inter-digestive housekeeper	Every 100 min
	Migrating cluster contraction	Inter-digestive housekeeper	Every 100 min
		Postprandial propulsion	5–10 per hr
	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
	Organised contraction Propagating, MMC	Slow anterograde and retrograde propulsion	1 every 35–50 min (dog)
	Non-propagating, MMC-like Giant migrating contraction	Rapid anterograde propulsion	2–4 every 24 hr

Abbreviations: MMC, migrating motor complex.

Clinical experience with BTX-A

We published the results of a pilot study on the use of BTX-A to treat chronic anal fissure in 10 patients (Gui *et al.*, 1994). The number of patients has now increased to 17 (9 females and 8 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 BOTOX® injected into the internal smooth sphincter and were followed-up for a period of two months (Table III). In 14/17 patients a healing scar was observed after two months.

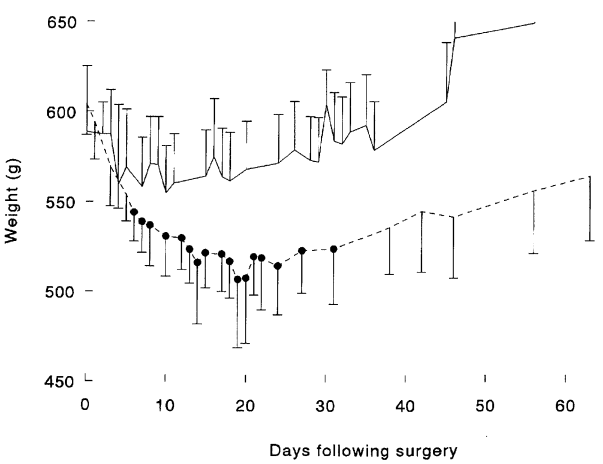

FIG. 1. Weights measured in two groups of rats following the injection of 20 units of BOTOX® (dashed line) or of saline (solid line) in the distal stomach. Filled circles in the lower plot indicate differences between the two groups that are statistically significant ($p < 0.01$).

Two of these patients then had a relapse, one of them was retreated successfully while the other requested to have surgery. Another patient with a fissure at two months was retreated with subsequent healing of the fissure. A further patient had a healing scar one month after treatment, but suffered a relapse which did not respond to further treatment.

Figure 3 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 7 and 30 days there is a statistically significant difference compared with baseline values at day 0. 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 interesting observation in so far as this is the first indication of a pathogenic rather than purely symptomatic indication for BTX-A. 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.

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® or placebo (saline) 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 already treated with saline will receive 20 units of BOTOX®, the patient already treated with the toxin will receive 25 units.

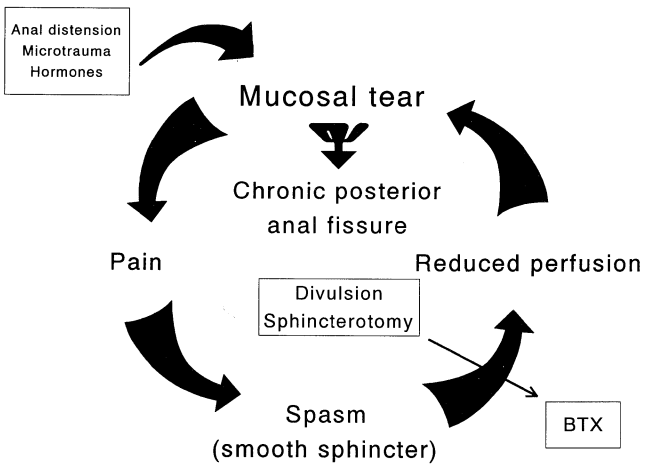

FIG. 2. Chronic posterior anal fissure is sustained by a vicious circle involving pain, which brings about a local spasm. The spasm is believed to reduce perfusion through the posterior anal artery, which in turn does not allow the mucosal tear to heal. Surgical interventions (e.g. divulsion, sphincterotomy) permanently reduce muscle strength and the effects of the local spasm. BTX acts with a similar mechanism but its effects are not permanent.

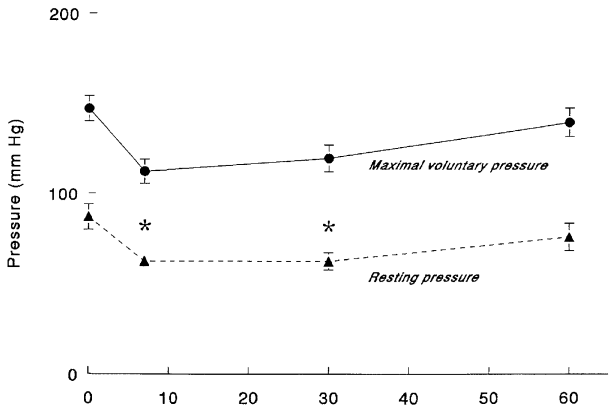

FIG. 3. Variation of resting pressure (triangles) and of maximum voluntary pressure (circles) following injection of BTX-A into the internal anal sphincter in patients affected by chronic posterior anal fissure. Asterisks indicate values that are significantly different from day 0 ($p < 0.01$).

New indications?

It is interesting to speculate on possible new indications for BTX-A.

- Is it 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-A may be used to reduce weight before surgery to reduce the operative risk.
- Is it possible to produce a targeted paralysis of the intestines? This is a possibility in selected cases when it is desirable to produce local paralysis and reduce propulsion.
- Is it possible to use BTX-A as a test drug of gastrointestinal motility? There are occasions when we need to test the functional ability of the gastrointestinal tract and this could possibly be done using a standardized test dose of BTX-A.
- Finally, local BTX-A injections could be used to treat hypertrophic pyloric stenosis of the new-born, thus avoiding surgery in infants.

In summing-up, we know that BTX-A is taken up by specific receptors, but I would like to know more about its selectivity for nerve terminals controlling gastrointestinal motility. We may need some animal experiments to map the affinity of different BTX serotypes for different nerve terminals along the length of the gastrointestinal tract.

DISCUSSION

Dr Friedman, Warsaw: Did you see any side-effects of BOTOX® in your patients?

Dr Albanese: Only one, a single case of incontinence.

Dr Friedman: Can you tell me a little more about how the injections were performed?

Dr Albanese: We injected three sites; injections were made laterally in the proximity of the fissure, not on it, and on the right and left sides and posteriorly in the proximity of the fissure. Originally this involved 5, 5 and 5 units but now we have increased this to a total of 20 units.

TABLE III. Time-course of signs and symptoms following treatment of chronic anal fissure with BTX ($n = 17$)

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

Professor Jankovic, Houston, TX: After fatigue and headache, constipation is the third most common problem for patients. Did you notice this in your patients? Some studies suggest that one of the reasons for constipation is increased sphincter contractility. Do you think that BTX-A may have a role in the treatment of constipation?

Dr Albanese: Yes, it is certainly a possibility. Dealing with constipation one has to choose one of the two theories of continence. If you choose the three sling theory, you will have three targets while with the flutter valve theory you only need to consider the puborectalis muscle as a target.

Professor Marsden: There have been reports of the use of BTX-A in the treatment of detrusor sphincter dyssynergia. How popular is that as a treatment, rather than just a report? I do not know any people using it regularly at present.

Dr Albanese: It is not very common. In our university there are some urologists who use it but have not published their experience. It is, however, very easy to perform at a urological check-up.

Dr Anton, Cannes: One problem in treating fissures is to know whether you are injecting smooth muscle or not. How can you tell?

Dr Albanese: In the case of the sphincter, I know I am injecting smooth muscle because it is superficial and can be seen easily. Striated muscle is much deeper. What I cannot be sure of is how much diffusion takes place. However, if you measure resting pressure and maximum voluntary pressure you can monitor muscle strength and use that as indirect evidence.

Dr Heinz, Zurich: We have had some experience injecting sphincter muscles; we initially used a large dose of BOTOX®, about 100 units in two ways: perineal and with cystoscopy. We were not able to paralyse the bladder muscles.

Dr Albanese: Are you sure you were in the muscle? It is very thin. How many injection points did you have?

Dr Heinz: One or two.

Dr Albanese: Chronic anal fissure is a special problem. The blood supply to the fissure is localized posteriorly. In our experiments we may not have weakened the anterior part of the smooth sphincter, but the treatment may have been sufficient to weaken the posterior part to allow more blood to reach the posterior mucosa and promote healing. If you want to weaken the sphincter you may need to inject at many sites, which may lead to more problems.

Professor Marsden: Are there any other unusual indications for BOTOX®? Some people use it to get rid of facial wrinkles, you can now cure anal fissure and lose weight. Does anyone know about using it for constant salivation in Parkinson's disease?

Dr Heinz: We have used it several times with good results. You only need 4 and 5 units injected in the angle of the mouth, which is easily accessible.

Professor Marsden: And how long does it last?

Dr Heinz: About 5 to 6 months.

Dr Dressler, Göttingen: BTX-A has been used in Göttingen for gustatory sweating problems, such as in Frey, syndrome, with injection into the temporal skin.

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