Towards safer treatments for benign anorectal disease: the pharmacological manipulation of the internal anal sphincter

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ABSTRACT

INTRODUCTION The internal anal sphincter (IAS) is an important structure that is responsible for the majority of resting tone of the sphincter complex. It has a central role in continence and damage to the muscle has serious implications. Injury is most frequently from obstetric trauma though iatrogenic injury from proctological surgery is also common. This review expands on how developments in understanding of the pharmacology of IAS might identify drug treatments as alternatives for proctological conditions such as anal fissure, avoiding the risk of sphincter injury. It also examines the role of pharmacology in treatment of those patients with established incontinence.

RESULTS Much of the basic physiology and pharmacology of the IAS has been established through *in vitro* analysis, particularly in the superfusion organ bath. Further analysis has been undertaken using animal models such the pig. Clinical trials have established the efficacy of a number of agents for reducing IAS tone including glyceryl trinitrate and botulinum toxin. These drugs are probably safer, but less effective, than surgery for sphincter spasm, as is seen in anal fissure, though surgery alone or in combination with drug treatment may be appropriate for some patients. *In vitro* analysis and small-scale clinical trials suggest that phenylephrine and methoxamine may have a role in treating patients with incontinence primarily attributable to inadequate IAS function.

CONCLUSIONS The pharmacology of IAS has been extensively studied in the laboratory, both *in vitro* and in animal models. In a short time, this laboratory work has been applied to clinical problems after testing in clinical trials. It is likely, however, that the best drugs and the optimal targets for manipulation have not yet been identified.

KEYWORDS

Internal anal sphincter – Glyceryl trinitrate – Botulinum toxin – Phenylephrine

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The internal anal sphincter (IAS) is anatomically continuous with the rectal circular muscle and forms a complete cylinder of muscle around the anal canal. As a smooth muscle structure, it is capable of maintaining a continuous tonic state, with little problem of fatigue. It is the single most important contributor to anal resting pressure. By contrast, the external anal sphincter makes only a small contribution to resting pressure but may be recruited during periods of increased risk to continence, such as occurs during coughing or straining.

The basal tone of the IAS is modified by a number of factors. Local reflexes enable the IAS to respond to the challenges of continence and defaecation. Amongst the most important of these reflexes is the recto-anal inhibitory reflex, which manifests as a relaxation of the IAS in response to rectal distension. This reflex is probably important in initiation of defaecation

and in the process of ‘anorectal sampling’. The latter process allows the rectal contents to come into contact with the sensitive anoderm and facilitates discrimination of flatus, liquid and stool without the anoderm becoming desensitised. Disruption of this reflex is often seen after surgery including anterior resection. Return of the reflex correlates closely with improvements in postoperative continence.

Sympathetic nerves to the IAS arise from the lower thoracic and upper lumbar segments and pass through the inferior and superior hypogastric plexuses and in fibres travelling with the inferior mesenteric artery. Background sympathetic nerve activity contributes to IAS resting tone. Parasympathetic fibres are derived from the second to fourth sacral roots and are distributed via the nervi erigentes (see Fig. 1). Activation of parasympathetic nerves reduces IAS tone.

Figure 1 Diagram of autonomic innervation of the internal anal sphincter. Internal anal sphincter tone reflects the sum of intrinsic myogenic tone of the sphincter itself (1), which is modified by local reflexes (2). Autonomic inhibitory input to the internal sphincter comes from parasympathetic nerves that synapse in the parasympathetic ganglia (3) and excitatory nerves from sympathetic nerves relaying in the sympathetic trunk (4). PreGSN, pre-ganglionic sympathetic nerve; PostGSN, post-ganglionic sympathetic nerve; PreGPN, pre-ganglionic parasympathetic nerve; PostGPN, post-ganglionic parasympathetic nerve.

The study of the internal anal sphincter *in vivo* and *in vitro*

An understanding of the pharmacology of the internal anal sphincter has been greatly facilitated by the superfusion organ bath.¹ This allows the study of isometric responses of isolated strips of smooth muscle suspended in a chamber pumped through with oxygenated solutions. The muscle strips may be subjected to electrical field stimulation from electrodes mounted within these chambers. The response of muscle strips is recorded via tension transducers. When stretched and allowed to equilibrate, IAS muscle strips develop tone – a feature that is common to many sphincteric smooth muscles. This tone is tetrodotoxin-resistant, implying that it is not dependent on neural input. This state of contraction is known as ‘myogenic tone’.

Application of noradrenaline, the post-ganglionic neurotransmitter of the sympathetic nervous system, to the superfusate provokes contraction mediated via α -adrenoceptors. This supports a dominant excitatory effect of sympathetic nerve input to the IAS. Acetylcholine is the neurotransmitter of the post-ganglionic parasympathetic nerves. Cholinergic agonists, such as carbachol, cause relaxation of IAS fibres *in vitro*. This effect is blocked by atropine indicating that it is mediated by muscarinic receptors (see Fig. 1) and by nitric oxide synthase inhibitors such as L-nitroarginine. This finding is consistent with nitric oxide as an important inhibitory neurotransmitter in the IAS and presumably the presence of acetylcholine receptors on these nitrergic nerves.²

The superfusion organ bath does not allow study of the interplay between the IAS and other factors in defaecation and continence. Fortunately, the study of anorectal physiology

in humans is well established as a clinical tool. Ethical considerations limit the usefulness of human studies, though the pig may become a useful model of defaecation and continence; there is some evidence that the pig is a continent animal, as it seems capable of deferring defaecation. Furthermore, studies in the superfusion organ bath have indicated that the physiological and pharmacological characteristics of pigs are similar to those of humans. Another potential animal model of continence and defaecation is the mouse, as this allows access to the field of knockout gene technology. There is already some evidence that the recto-anal inhibitory reflex may be abnormal in mice with homozygous mutations in the neuronal nitric oxide synthase gene.⁵

IAS dysfunction in colorectal disease

EXCESSIVE IAS CONTRACTION

Excessive contraction of the IAS is seen in a number of proctological conditions. In 1835, Brodie described how 'in connexion with spasmodic contraction of the sphincter muscle, you will frequently find a small ulcer of the mucous membrane of the rectum'.⁴ This sphincter spasm is thought to be central to the pathophysiology of anal fissure. The degree of spasm in anal fissure is sufficient to cause ischaemia of the anoderm and prevent healing of the anal fissure leading to chronicity.⁵ IAS spasm is not limited to patients with anal fissure; it may also be seen in other conditions including haemorrhoidal disease and after proctological surgery.

INADEQUATE IAS CONTRACTION

Faecal incontinence is a common condition that may be disabling and cause social isolation. IAS dysfunction may contribute to incontinence. The aetiology of sphincter dysfunction includes primary degeneration of the IAS, sphincter myopathy or as part of connective tissue disorders such as systemic sclerosis. Radiotherapy, most commonly in the context of rectal or prostate cancer, may also impair IAS function. More frequently, however, the IAS is damaged either as a consequence of childbirth or surgery.⁶

Surgery and modification of internal anal sphincter function

EXCESSIVE IAS CONTRACTION

The simplest and most effective means of reducing internal sphincter tone is surgery. This can either take the form of manual dilatation of the sphincter or lateral internal sphincterotomy. Both are commonly employed as treatments for anal fissure.

Manual dilatation of the anus is falling out of favour as a procedure. Incontinence may be seen in around one-quarter of patients. Endo-anal ultrasound demonstrates sphincter

Figure 2 Endo-anal ultrasound appearances after manual dilatation of the anus (left) showing fragmentation of the internal anal sphincter (deficient between 2 and 3 o'clock and 4 and 8 o'clock) and lateral internal sphincterotomy (right) showing a deficient internal sphincter between 2 and 6 o'clock with bunching of the sphincter fibres on the contralateral side.

defects in a substantial number of patients, with fragmentation of the IAS being the most common abnormality (Fig. 2).

Lateral internal sphincterotomy aims, by definition, to divide the IAS. The length of division is variable with some authors advocating division for the length of the fissure, others to the dentate line. Endo-anal ultrasound, however, demonstrates that the length of sphincter division may extend much further than the surgeon intended (Fig. 2). Often the whole length of the sphincter is inadvertently divided, especially in women in whom the IAS is shorter.⁷

INADEQUATE IAS CONTRACTION

The surgical options for patients with IAS functional deficiency are more limited. Attempts at surgical repair of structural damage to the IAS have not generally met with much success. Endo-anal ultrasound usually shows persistence of the sphincter defect after surgery.⁸ Injectable silicon biomaterials have also been used for patients with a weak or disrupted IAS, with good results in some patients.⁹ Although sacral nerve stimulation has proven to be effective for many patients with an anatomically intact but

functionally deficient IAS, the mechanism of action of this treatment does not appear to be through simple increase in sphincter resting tone.¹⁰

Pharmacological modification of internal anal sphincter function

EXCESSIVE IAS CONTRACTION

An understanding of the pharmacology of the IAS has facilitated the development of agents that reduce tone transiently. Glyceryl trinitrate (GTN) is a nitric oxide donor that can be applied directly to the anal canal in the form of a paste. There have been some reports of good efficacy of GTN paste in the treatment of anal fissure,¹¹ though subsequent studies have been more disappointing.

Some authors suggest that surgery should remain the first-line treatment for anal fissure, though they usually disregard the possibility that surgery may lead to long-term problems with continence. There have been four randomised trials comparing GTN paste to lateral internal sphincterotomy. Three of these demonstrated the superiority of sphincterotomy over GTN paste,^{12–14} whilst the other small trial has suggested little difference between the two approaches (Table 1).¹⁵

Fissure healing is the primary end-point in all of these studies and, in each case, forms the basis of the power calculations of the trials. The implication of this is that the authors believe that GTN needs to have similar or better healing rates than sphincterotomy to justify adoption as first-line treatment. However, surgery is a very effective treatment for anal fissure, a fact indirectly acknowledged by the authors of three of these trials in their assumption of a 95% healing rate after sphincterotomy, when calculating power scores. Pharmacological agents were developed because of concerns about incontinence after surgery and the belief that no permanent impairment of sphincter function results from pharmacological agents. However, not one of these four studies was powered to look at differences in continence. Only one trial used continence scores and none used quality-of-life measures. The longest follow-up was 2

Table 1 Healing and incontinence rates in four randomised trials comparing lateral internal sphincterotomy with glyceryl trinitrate paste

Trial	Healing after LIS	Healing after GTN	Significance	Incontinence	Follow-up (median)
Oettle (1997) ¹⁵	12/12	10/12	$P = 0.239$	0/12	22 months
Richard <i>et al.</i> (2000) ¹²	34/38	13/44	$P < 0.001$	0/38	6 months
Evans <i>et al.</i> (2001) ¹³	26/27	20/33	$P = 0.001$	0/34	5 months
Libertiny <i>et al.</i> (2002) ¹⁴	34/35	16/35	$P < 0.001$	1/34	24 months

LIS, lateral internal sphincterotomy; GTN, glyceryl trinitrate paste.

years and in two trials it was 6 months or less (Table 1). This is important because incontinence may only manifest several years after sphincterotomy. The patient's initial relief from symptoms of the fissure may lead him or her to ignore minor incontinence. Furthermore, borderline sphincter function may only be unmasked as anal canal pressure drops further with age or is compounded by subsequent obstetric injury. None of these studies performed endo-anal ultrasound or manometry as short-term surrogate markers for future risk of incontinence.

GTN has a number of disadvantages including tachyphylaxis and headaches. There is some evidence that calcium channel antagonists in paste form are better tolerated, though healing rates are similar. However, compliance remains an issue, not least because they require repeated topical application over many weeks.

Botulinum toxin is finding a place in the treatment of many conditions in medicine, through its ability to provide a temporary blockade of acetylcholine release from the pre-synaptic nerve terminal of striated muscle. It may be a more effective method of healing anal fissures than GTN paste. In a trial randomising 50 patients between botulinum toxin and GTN, injection was found to heal 96% of patients whilst paste only healed 60%. Cross-over treatment of nine of the GTN failures with botulinum toxin resulted in healing of 100% of patients.¹⁶

There are some paradoxes with use of botulinum toxin. Most of its documented effects are on striated muscle, yet the pathology in anal fissure is thought to relate predominantly to the smooth muscle IAS. Clinicians have injected the toxin, therefore, variously into the external sphincter, the internal sphincter and even the intersphincteric space. Anorectal physiology after botulinum toxin injection suggests that the predominant effect of the drug is on resting pressure and, by implication, its action is probably on the IAS. However, acetylcholine relaxes IAS fibres *in vitro* and so inhibition of acetylcholine release from the presynaptic nerve terminal by botulinum toxin would be expected to cause a rise, and not a fall, in anal resting pressure.

My own work aimed to study the effects of botulinum toxin on porcine IAS fibres *in vitro*.¹⁷ Porcine IAS muscle strips were studied in a superfusion organ bath (see above) and were found to develop myogenic tone. Electrical field stimulation (EFS) can be applied with parameters that induce first a relaxation response, blocked by L-nitroarginine, indicating that it is nitrergic in nature and then a contractile response, blocked by guanethidine, consistent with this being mediated by noradrenaline (Fig. 3). All responses to EFS could be blocked by tetrodotoxin, a nerve toxin, confirming that EFS was producing these effects by nerve stimulation.

Application of botulinum toxin to these strips followed by nerve stimulation resulted in a decreased contractile response to EFS. This is consistent with an effect of botulinum toxin on excitatory sympathetic input to the IAS. The nicotinic agonist 1,1-dimethyl-4-phenylpiperazinium iodide (DMPP) also produces IAS muscle strip contraction though its actions are blocked both by guanethidine and botulinum toxin. The most likely explanation for this finding is that DMPP is stimulating nicotinic sympathetic ganglia within the IAS. In turn, botulinum toxin is probably inhibiting noradrenaline release from the post-synaptic sympathetic nerves.

One concern that we had about this work was whether it provided a reliable model of how botulinum toxin worked *in vivo*. The clinical effects of botulinum toxin are not seen for several days and this may reflect migration of the toxin from its site of injection to its site of action. Furthermore, muscle strips can be kept alive in the organ bath for only about 6 h; therefore, the *in vitro* studies above may not be elucidating a clinically relevant action seen in patients. The second stage of my work, compared IAS muscle response *in vitro* between pigs pretreated with botulinum toxin injection and pigs receiving saline injection showed that muscle strips from treated pigs develop less myogenic tone. They also have a smaller amplitude of contraction in response to EFS with parameters known to stimulate sympathetic nerves, supporting the hypothesis that botulinum toxin acts on sympathetic nerves in the IAS (Fig. 4).¹⁸

The action of botulinum toxin on the IAS provides a rationale for using this as the site of injection of the drug. However, our experience in Oxford of using botulinum toxin for anal fissure produced disappointing healing rates.¹⁹ We had observed that patients with very fibrotic fissures seemed to be less likely to heal. We undertook a manometric study of patients with anal fissure and found that many of them in fact had normal or even occasionally low sphincter pressures.²⁰ We reasoned that the aetiology of fissure in these patients could not be spasm-induced ischaemia and that fibrosis might also play a role. The development of fissurectomy combined with injection of botulinum toxin was based on a perceived need to address both fibrosis and spasm in patients with refractory anal fissure. Fissurectomy involved excision of the fissure edges

and the sentinel pile with curettage of the fissure base without disruption of the IAS itself. In our experience, it is effective in over 90% of patients with persistent anal fissure refractory to simpler treatments.²¹

Selective inhibition of different components of the anal sphincter complex with an oral drug, free of side effects is a future goal of research in this field. One class of drugs that might fulfil this role are the phosphodiesterase inhibitors, which have recently received much interest as a treatment for impotence. These drugs prevent the action of phosphodiesterases which, in turn, hydrolyse the intracellular second messengers adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP). There are a number of different subtypes of phosphodiesterases, expressed in different levels in the various organs of the body, and many have specific inhibitors. In Oxford, we have shown that phosphodiesterase inhibitors are effective in causing relaxation of IAS strips *in vitro*.²² They also have differing efficacy between IAS muscle and rectal circular muscle even though these two structures are anatomically continuous with each other. Further clinical studies are needed to elucidate if phosphodiesterase inhibitors will provide an oral agent with few side effects that selectively reduces IAS tone.

Future research in this field will probably examine clinical application of pharmacological measures to reduce IAS tone for diseases other than anal fissure. For example, patients with thrombosed haemorrhoids often have IAS spasm. Use of topical agents, such as GTN paste, may also reduce pain after haemorrhoidectomy. It has also been suggested, variously, that either hypertonia of the IAS or the anal longitudinal muscle might be important in the patho-

physiology of haemorrhoids. There is evidence from a randomised trial to suggest that use of GTN paste before transanal stapled anastomosis is associated with less frequent need for dilatation in order to insert the stapler, less effect on sphincter pressures and better continence.²³

INADEQUATE IAS CONTRACTION

Pharmacological treatments to increase sphincter tone have been based on adrenergic agonists. Phenylephrine gel has been evaluated in a number of small trials. It has been shown to increase maximum anal canal pressure in normal volunteers and, at higher doses, to increase anal resting pressures significantly in incontinent patients with an intact IAS on endo-anal ultrasound. Whilst phenylephrine gel has been shown to improve continence amongst ileo-anal pouch patients with structurally normal sphincters, these results have not been mirrored in non-pouch patients with incontinence.²⁴

It has been suggested that the lack of efficacy with phenylephrine amongst some patients results from not using a high enough dose of the drug. Dermatitis from drug application has also been a problem. In Oxford, we have evaluated an alternative adrenergic agonist, methoxamine, *in vitro*²⁵ and it appears to be more potent than phenylephrine. Further data from clinical trials on this more potent alternative are awaited.

The ideal drug for treatment of incontinence would be in oral form. Loperamide is an oral drug already widely used as a treatment for faecal incontinence. It is generally considered that its main effect is to modify stool consistence, though it has also been shown to increase anal tone²⁶ and to modify the recto-anal inhibitory reflex. Amitriptyline has also been shown in an open-label study to improve incontinence scores and reduce bowel frequency.²⁷ The mechanism of action of this drug is thought to be through its anticholinergic and serotonergic properties manifesting as a decrease both in amplitude and frequency of rectal motor complexes. In this study, amitriptyline also improved anal canal pressures. Both of these drugs need to be evaluated further in clinical trials. A better understanding of the mechanism of action of sacral nerve stimulation may also provide clues for future drug development. Whilst the effects of sacral nerve stimulation on incontinence symptoms appear to be striking, there is little impact on anal resting pressures. Anal pressure slow wave activity may be enhanced and spontaneous anal relaxations reduced. Some studies have reported an increase in duration and size of anal squeeze pressure. Sacral nerve stimulation also appears to have effects on colonic and rectal motility with perhaps an additional modification of rectal sensation.²⁸

Conclusions

Pharmacological manipulation of the IAS remains in its infancy. In terms of clinical applications, the treatment of anal

fissure is perhaps the most developed area. Pharmacological therapies are simple to administer for this disease. They do not preclude surgical treatment in the future and may avoid it altogether. Pharmacological treatments do not appear to have long-term deleterious effects on continence. A reasonable strategy for this disease might be the immediate prescription of a topical therapy to all patients. Failures can be treated with botulinum toxin, perhaps combined with fissurectomy, though the exact role of fibrosis in anal fissure needs additional investigation. The role of pharmacological reduction of sphincter tone in the treatment of other conditions, such as haemorrhoidal disease, requires further evaluation.

Efforts to increase IAS tone in patients with incontinence have been less successful. This might simply reflect the fact that the correct drug has not yet been found or that dosage and timing of application has not been established. Identifying the subgroup of patients with incontinence likely to benefit from pharmacological augmentation of IAS tone is also a challenge. In most incontinent patients, the aetiology is multifactorial and combining drug therapies and surgery may be the recommendation of the future.

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