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Current Concepts on Pathophysiology, Diagnosis and Treatment of Diffuse Oesophageal Spasm

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Abstract

Diffuse oesophageal spasm is a functional oesophageal motility disorder of unknown aetiology, which appears to be due to a disturbance of the normal pharmacological timing of propulsive contraction occurring in the oesophageal body after swallowing. The lack of pathophysiological understanding may be due to the fact that there is more than one pathophysiological pathway causing symptoms of diffuse oesophageal spasm. Barium studies, oesophageal scintigraphy and fiberoptic examination can be helpful in finding the correct diagnosis, but manometry is still the gold standard of diagnostic procedures.

Similar to other spastic oesophageal motility disorders, pharmacological treatment of diffuse oesophageal spasm includes nitrates, calcium antagonists, anticholinergics and antidepressants with varying beneficial effects. Botulinum toxin, which provides sufficient treatment as measured by symptom score and manometric patterns in patients with achalasia, was recently evaluated for the treatment of diffuse oesophageal spasm in small patient selections with promising results.

The major function of the oesophagus is to transport material from the pharynx to the stomach. Diffuse oesophageal spasm, which was first described by Osgood in 1889, represents a neuromuscular abnormality that can lead to painful swallowing, impairment of the transport process or both. Diffuse oesophageal spasm is a rare disease with an incidence of 0.2/100 000 per year. Most patients are more than 50 years of age at first manifestation.[1]

Patients seek medical attention because of chest pain, dysphagia and regurgitation. Very hot or cold liquids may aggravate the symptoms. Dysphagia is usually transitory and nonprogressive and occurs with both solids and liquids. The chest pain associated with the oesophageal spasms may be severe and wake the patient during sleep. Chest pain also occurs in the absence of dysphagia or regurgitation and this pain is hardly distinguishable from coronary heart disease or other causes of noncardiac chest pain.[2,3]

The aetiology of diffuse oesophageal spasm is still unknown. It is characterised by multiple, spontaneous, nonpropulsive contractions and by swallow-induced repetitive contractions of simultaneous onset, large amplitude and long duration in manometric examination. In some patients, these motor abnormalities are accompanied by an abnormal function of the lower oesophageal sphincter. Physiological studies suggest that this disorder of the oesophagus involves both sensory and motor mechanisms since the oesophagus is sensitive to cholinergic, mechanical and acid stimuli, emotional states and olfactory stimuli, and there are single cases reporting a reversal through inhalation of ipratropium bromide.[4,5] This is in agreement with the fact that patients with other oesophageal motility disorders, such as achalasia, show generalised autonomic dysfunction.[6]

Clinical and manometric patterns of diffuse oesophageal spasm may overlap with achalasia. There are reports that patients may progress from diffuse oesophageal spasm to achalasia and from other spastic nonspecific oesophageal motility disorders to diffuse oesophageal spasm, suggesting that these spastic oesophageal motility disorders overlap clinically and pathophysiologically.[7]

There are only a few reports of clinical trials treating diffuse oesophageal spasm. In general, anticholinergics (propantheline bromide, cimetropium bromide, ipratropium bromide), nitrates, calcium antagonists and recently botulinum toxin have been used with varying results.[4,8-14]

It is worth noting that medications used for reduction of hypercontractile disorders predispose patients to gastro-oesophageal reflux disease (GORD) and therefore it is advisable to add an antisecretory drug into therapy, preferably a proton pump inhibitor, at least at the onset of the therapy.[15] On the other hand, GORD is a frequent underlying disorder in many oesophageal motility disorders and this form of acid-induced motility disorder can imitate the clinical, radiological and manometric features of diffuse oesophageal spasm. Therefore, 24-hour pH-monitoring should be completed before any treatment trial because in these patients symptoms respond to acid suppression therapy.[16,17]

For diffuse oesophageal spasm, progress has been made to establish a precise diagnosis but the pathophysiology of this disorder is still poorly understood and therefore therapeutic options are still rare.

1. Pathophysiology and Classification

Diffuse oesophageal spasm is a functional oesophageal motility disorder of unknown aetiology but it appears to be due to a disturbance of the normal pharmacological timing of propulsive contraction occurring in the oesophageal body after swallowing.

Transport of food through the oesophagus into the stomach is mainly achieved by a peristaltic wave that starts in the pharynx and progresses down the oesophagus until it reaches the cardia. The functional basis for this peristaltic wave has been attributed to the latency period between the onset of a swallow and the sudden change in the pressure wave of the contraction of oesophageal smooth muscle.[18]

Theories about the origin of the latency of oesophageal contraction necessary for the propulsive coordination of contraction are several-fold:

- Propulsion may be coordinated by a vagal gradient from the proximal to distal oesophagus or
- By an increasing cholinergic latency from the proximal to distal oesophagus[19] or
- By a gradient in inhibitory nitric oxide (NO)-mediated innervation since NO-synthase blockers cause an increase in propulsion latency.[20]

1.1 Cholinergic Mechanisms

Although the pathophysiology of diffuse oesophageal spasm is unknown, physiological studies suggest that, in this disorder, the oesophagus is sensitive to cholinergic stimuli.[4,21] In humans, contraction in the upper striated third of the tubular oesophagus is mainly controlled by vagal-cholinergic mechanisms, whereas the distal part of the oesophagus, containing smooth muscle, is under the control of autonomic-cholinergic and autonomic–non-adrenergic, non-cholinergic mechanisms.[22] Normal oesophageal motor function is characterised by a quiescent oesophagus at rest, which is stimulated by swallows that evoke peristaltic contractions able to propel food boluses from the pharynx to the stomach.

In patients with diffuse oesophageal spasm, manometric findings are characterised by the absence of propulsive contractions. The simultaneous contractions found in patients with diffuse oesophageal spasm can be differentiated into two different types based on whether they are evoked by swallows or whether they are spontaneous.[23] Spontaneous contractions could be caused by an abnormal spontaneous acetylcholine release or by an imbalance of cholinergic excitatory and inhibitory mechanisms, since they can be abolished by atropine administration.[23] Swallow-induced peristaltic sequences originate in the swallowing centre, are transmitted by the vagal nerve and reach the entire length of the oesophagus about the same time and activate intramural neuromuscular units.[24,25] This causes an initial inhibition or hyperpolarisation of the smooth muscle whose duration increases aborally, followed by a depolarisation and contraction that is generated after the stimulus is discontinued.[23,26] Since simultaneous contractions in patients with diffuse oesophageal spasm are sometimes confined to the distal 10cm of the tubular oesophagus, they are unlikely to be caused by an abnormal stimulation by the central nuclei. They are more likely to result from an inappropriate response to vagal stimuli of the intramural neural units that innervate the oesophageal smooth muscle segments.

The functioning of oesophageal emptying/clearance is strongly related to the latency period between the onset of a swallow and contraction of oesophageal circular muscle.[18,27] The duration of the latency period increases progressively from the proximal to the distal oesophagus, and this latency gradient is one basis of oesophageal peristalsis.[18,27,28] In the early phase of the latency period, a non-adrenergic, non-cholinergic (NANC) transmitter is released causing initial hyperpolarisation and inhibition of oesophageal smooth muscle.[29]

The latency period is guaranteed by the functioning of the interplay of excitatory and inhibitory influences. Increased excitation would lead to contractions of higher force and duration rather than influencing the latency period. Therefore, it seems reasonable that the defective pathway in patients with swallow-related simultaneous contractions is the inhibitory pathway. An important finding is that the anticholinergic atropine is potent in reducing the force and duration of the swallow-induced oesophageal contractions but that it can not simultaneously transform them into peristaltic contractions, suggesting that an excess of cholinergic excitatory stimulation does not contribute to their pathogenesis and further suggesting that acetylcholine is not involved in generating the latency, causing the sequential peristalsis.[30]

However, atropine decreases the frequency of spontaneous simultaneous contractions, as well as their duration and force, and since atropine can abolish these spontaneous simultaneous contractions it seems possible that they are due to release

of acetylcholine independent of the deglutition reflex.[23]

1.2 Nitrergic Mechanisms

The nature of the inhibitory neurotransmitter and its role in the latency period has not been established, but there is convincing evidence that NO or a related compound is implicated in the modulation of the peristalsis of the oesophageal body.[31,32] Inhibition of endogenous NO generation by inhibition of the NO-synthase by L-NAME (N-nitro-L-arginine methyl esther) shortens the latency period of propulsive contractions induced by swallowing throughout the oesophagus to the point that oesophageal contractions become nearly simultaneous.[32] An involvement of NO in the development of a latency period and the amplitude of oesophageal peristalsis has been demonstrated in the opossum oesophagus where administration of the NO-synthase blocking compound L-NAME or L-NNA (NG-nitro-L-arginine) reduced the latency period of oesophageal body contractions and reduced bolus propagation time in the middle and the distal part of the oesophagus in response to swallowing or vagal stimulation.[32,33]

Inhibition of NO-synthase also antagonised relaxation of the lower oesophageal sphincter induced by swallowing or vagal stimulation and was reversed by L-arginine, the substrate of NO-synthase.[32] These data strongly suggest an important role for NO in the regulation of oesophageal peristaltic contraction of the distal part of the oesophagus and relaxation of the lower oesophageal sphincter.

The unusual tolerance of nitrates in patients with diffuse oesophageal spasm suggests a general malfunction in endogenous NO synthesis and/or degradation in this patient selection as the possible underlying pathomechanism.[34]

Initially, the therapeutic use of nitrates in oesophageal motility disorders was based on the clinical experience that amyl nitrate given to patients with achalasia during a barium swallow will induce an immediate relaxation of the lower oesophageal sphincter region.[35]

The great importance of endogenous 'nitrates' in form of NO for oesophageal motility has been shown recently.[22,33] In the smooth circular muscle of the human oesophagus, NO acts as an inhibitory NANC transmitter as demonstrated in experiments with electrical field stimulation. NO-synthase can be localised in nerves within the lower oesophageal sphincter and the oesophageal wall, implicating an NO action in this region.[36] The clinical importance of these endogenous nitrates has not been established yet.

In a clinical trial in healthy volunteers, intravenously administered recombinant human haemoglobin acting as an NO scavenger increased oesophageal peristaltic velocity, produced a significant increase in the number of spontaneous, simultaneous contractions, increased the amplitude and duration of contractions, and inhibited lower oesophageal sphincter relaxation suggesting an important physiological role of NO in oesophageal peristalsis and in lower oesophageal sphincter relaxation.[37] Furthermore, these data suggest that disorders of oesophageal motor function may result from defects in NO-neuromuscular communication.[37] This is emphasised by the finding that, in humans, blockade of NO-synthase by L-NMMA (NG-monomethyl-L-arginine) increases the peristaltic velocity and the amplitude of peristaltic contractions suggesting an involvement of NO in the timing of human oesophageal peristalsis.[20]

The reports of the effect of nitrates on the oesophagus have often been conflicting since some investigators have noted no objective response in symptomatology and motility patterns,[38] and others observed symptomatic relief and control of oesophageal spasm after nitrate administration. The reason for this may be the still unknown aetiology of diffuse oesophageal spasm, which may represent a variety of underlying disorders. More recent investigations suggest that there may be at least two subgroups of diffuse oesophageal spasm. One group associated with pathological GORD where nitrates are less effective in improving symptoms and controlling symptom scores,[39,40] and the other group without pathological GORD, which are good re-

Table I. Manometric criteria of diffuse oesophageal spasm and conceivable subclassification according to lower oesophageal sphincter (LOS; LES) function

Classic criteria	Simultaneous contractions in >30% of wet swallows Prolonged duration (>6 sec) Double or multiple peak contractions Increased contraction amplitude (>160 mmHg) LES can be normal or have high pressure or insufficient relaxation or both
Subclassification	1a) regular LES-pressure and LES-relaxation 1b) regular LES-pressure and impaired LES-relaxation 2) GORD + regular or decreased LES-pressure

GORD = gastro-oesophageal reflux disease.

sponders to therapy with nitrates based on long term symptom scores and motility patterns.[39] The group where GORD is not the underlying disorder may be further subdivided into diffuse oesophageal spasm with regular lower oesophageal sphincter function and diffuse oesophageal spasm with impaired lower oesophageal sphincter relaxation (table I).

1.3 Reflux Mechanisms

For diffuse oesophageal spasm where pathological GORD may be the underlying disorder, or at least a cofactor triggering oesophageal spasm, control of reflux with acid blocking drugs and management of oesophagitis seems to be the treatment of choice and additional treatment with nitrates may be beneficial as an adjunct to antireflux therapy.[39] This form of diffuse oesophageal spasm should be classified as an acid-related motility disorder.

Because of the pathophysiology of reflux, nitrates alone will aggravate the reflux and, therefore, promote the disease since nitrates reduce the lower oesophageal sphincter via smooth muscle relaxation. The subgroup of patients with diffuse oesophageal spasm with impaired lower oesophageal sphincter relaxations can be successfully treated by pneumatic dilatation or bouginage of the sphincter.[41] This fact has also been partially responsible for the hypothesis that lower oesophageal sphincter dysfunction may play an important physiological role in various oesophageal motor disorders;[42] however, more recent data suggest that there might be a subgroup of patients with diffuse oesophageal spasm where the disorder transforms into achalasia.[43] Since the subgroups of diffuse oesophageal spasm present different motility characteristics suggesting different underlying disorders, it seems reasonable that simply classifying these disorders as diffuse oesophageal spasm does not hold true.

2. Diagnosis

Diagnosis of diffuse oesophageal spasm is generally made by typical radiological and manometric findings. However, since tertiary oesophageal contractions can also be found in healthy people, the diagnosis should only be made when the patient presents typical symptoms. Since symptoms overlap, heart disease should always be excluded by a stress-electrocardiogram or a coronary angiogram before oesophageal investigations. Furthermore, other primary oesophageal motility disorders (e.g. achalasia; hypercontractile oesophagus) have to be excluded.

2.1 Manometry

The diagnosis of diffuse oesophageal spasm is generally made by manometry as, currently, the formal criteria for diagnosis are exclusively manometric in nature. The manometric criteria of diffuse oesophageal spasm are summarised in figure 1 and table I. The manometric diagnosis is made by the finding of nonpropulsive contraction sequences after swallows of small water boluses represented by simultaneous onset of contraction at multiple levels in the oesophagus or by prolonged or multiphasic contractions.[44] Nonperistaltic contractions are determined from the manometric tracing by establishing the onset of contraction at different levels and calculating propagation velocity.[45] Calculating contraction velocity using contraction wave upstrokes over 5 to 10cm of oesophageal length established an average velocity varying from 2 to

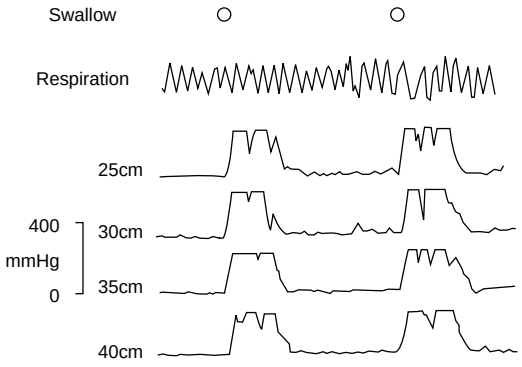

Fig. 1. Image showing simultaneous contractions of prolonged duration, multiple peak contractions and an increased contraction amplitude as the typical manometric findings in a patient with diffuse oesophageal spasm.

4 cm/sec in healthy volunteers.[46] The value can be used as an objective criteria but the velocity of intermittently nonperistaltic contractions is often well above this threshold.

The precise percentage of nonperistaltic contractions required for diagnosis remains a matter of debate. The upper limit must be <100% since some normal peristalsis is required or the diagnosis of severe hypomotility or achalasia must be considered. The lower limit, however, remains the subject of debate since simultaneous contractions occur in up to 10% of swallows of healthy volunteers.[47] An uncertainty remains in declaring the diagnosis of diffuse oesophageal spasm solely because the normal limit has been exceeded. A secure diagnosis of a relevant motor disturbance can be made when 30% or more of swallows are abnormal. In patients with normal motility patterns but presenting with the typical symptoms, a provocation test with drugs (e.g. edrophonium 10mg intravenously) or a 24-hour manometric examination may be of help to find the precise diagnosis.[48,49] However, there are patients with clinical features of diffuse oesophageal spasm occurring intermittently where repeated diagnostic procedures are needed to give a precise diagnosis.

2.2 Other Diagnostic Procedures

In patients with dysphagia or non-cardiac chest pain, a fiberoptic and a radiographic examination has to be done before manometry to rule out other underlying diseases (e.g. carcinoma, Barrett's oesophagus). Radiographic findings in patients with diffuse oesophageal spasm can also lead to the correct diagnosis.[50,51] Radiographic findings in barium studies include trapped barium in poorly sequenced peristaltic waves producing the appearance of corkscrewing or diverticula, an aspect formerly known as Barsony's oesophagus[52] (fig. 2). Furthermore, radiographs may show simultaneous or tertiary contractions, but simultaneous and tertiary contractions can also occur in healthy individuals and should be regarded as normal when symptoms are missing. The degree of barium retention is not as profound as in achalasia. Barium studies are hampered by a low sensitivity for diffuse oesophageal spasm since some patients with diffuse oesophageal spasm at manometry have had unremarkable barium studies.[51] Furthermore, computerised tomography (CT) investigation together with the typical symptoms can lead to the correct diagnosis since in patients with diffuse oesophageal spasm a thickening of the oesophageal wall can be found.[53]

Oesophageal scintigraphy is another sensitive examination for oesophageal retention and impaired bolus transport. Nevertheless, patients with barium studies or scintigraphy suggesting diffuse oesophageal spasm often require manometry for differentiation of the different oesophageal motility disorders. A fiberoptic examination has to be included in the diagnostic procedures to rule out other diagnoses (fig. 3).

Since it has been recognised that some cases of diffuse oesophageal spasm are associated with GORD and may improve when treated with antireflux measures, all patients with diffuse oesophageal spasm should undergo 24-hour pH-monitoring to rule out GORD.

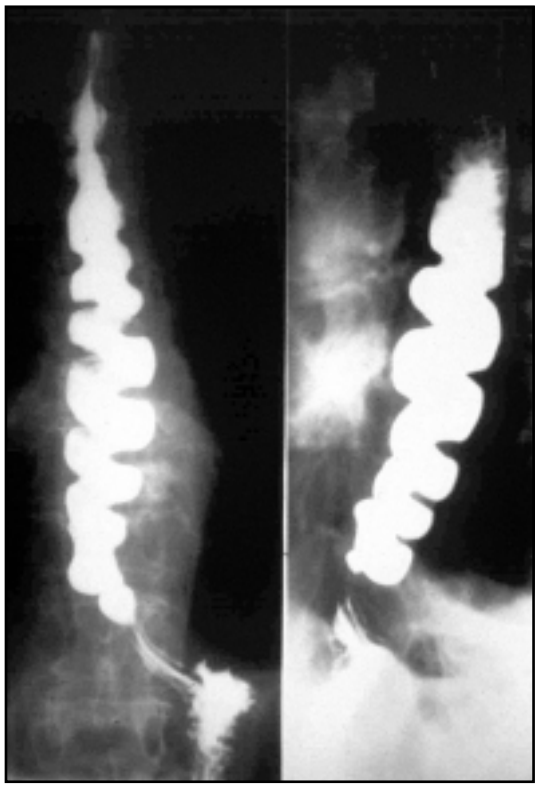

Fig. 2. Roentgenograms taken during a barium swallow in a patient with diffuse oesophageal spasm showing the typical trapped barium in poorly sequenced peristaltic waves, producing the appearance of corkscrewing or diverticula.

3. Pharmacological Treatment

Medical treatment of patients with diffuse oesophageal spasm similar to other spastic oesophageal motility disorders remains a challenge and involves the use of smooth muscle relaxants, calcium antagonists, psychotropic drugs and, more recently, botulinum toxin (tables II and III). Further therapeutic options include pneumatic balloon dilatation, bouginage and surgical long-myotomy.[62]

3.1 Nitrates

Nitrates have been reported to effectively reduce manometric findings and symptoms in casuistic reports and non-blind trials. Therefore, long-acting nitrates were proposed as a long term therapy.[9] In a clinical trial of 5 patients with diffuse oesophageal spasm, intravenous nitroglycerin (glyceryl trinitrate) 100-200 μg/kg decreased the duration of contractions and relieved symptoms while L-arginine caused no effect on oesophageal motility.[34] In contrast, in a double-blinded, placebo-controlled trial in 8 patients with noncardiac chest pain, chronic oral application of L-arginine over 6 weeks decreased the frequency and intensity of pain episodes, without affecting motility patterns.[63]

Molsidomine is effective in reducing pain sensation under basal conditions and after edrophonium provocation in patients with noncardiac chest pain. Therefore, molsidomine might be a useful therapeutic tool in patients with hypercontractile oesophageal motility disorders like diffuse oesophageal spasm,[13] although in other functional studies molsidomine had no influence on the tubular oesophagus.[64]

The mode of application might be of importance in the clinical effects of nitrates. Similar to the use of nitrate therapy in cardiology, there could be a need for a nitrate-free interval of 12 to 16 hours to avoid tachyphylaxy. Long term nitrate application

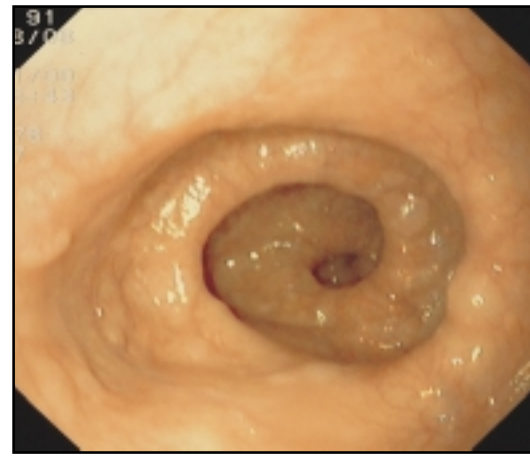

Fig. 3. Upper gastrointestinal endoscopy in a patient with diffuse oesophageal spasm showing the typical view into the corkscrew-oesophagus.

Table II. Clinical trials of pharmacological treatment of diffuse oesophageal spasm

Investigator	Type of study	No. of patients	Dose	Lower oesophageal sphincter pressure	Amplitude of oesophageal contractions	Symptom-score
Traube et al.[54]	Consecutive	9	Nifedipine 20mg	↓	↓	
Nasrallah[55]	Placebo-controlled; randomised; cross-over	4	Nifedipine 10mg	↓	↓	+
Thomas et al.[56]	Nonblind	6	Nifedipine 10-20mg		↓	+
Clouse et al.[57]	Placebo-controlled; double-blind	29	Trazodone 100-150mg	–	–	+
Konturek et al.[34]	Consecutive	5	Nitroglycerin 200 μg/kg/h	↓	–	+
Swamy[39]	Consecutive	12	Nitrates variable doses		↓	±
Drenth et al.[58]	Placebo-controlled; double-blind; crossover	8	Diltiazem 60mg			+

↓ indicates decreased; – indicates unaffected; + indicates symptomatic improvement.

is limited by the frequent occurrence of adverse effects since many patients complain of headache and tachycardia.

3.2 Calcium Antagonists

There are at least 3 major classes of calcium channels which regulate Ca^{2+} influx into the cell. L-type calcium antagonists are potent inhibitors of membrane potential dependent contractions *in vitro* and *in vivo*. Changes in intracellular Ca^{2+} are directly linked to the contractile process of striated and smooth muscle.

In healthy volunteers, as well as in patients with hypercontractile disorders of the oesophagus such as achalasia, diffuse oesophageal spasm and hypercontractile oesophagus, calcium antagonists have been shown to reduce lower oesophageal sphincter pressure and oesophageal contraction amplitudes. The decrease of sphincter pressure correlates well with the corresponding plasma drug concentration.[55,65,66]

A systematic comparison of various calcium antagonists showed that nifedipine is more potent than nitrendipine and nisoldipine and that these are more potent than verapamil and diltiazem in inhibiting oesophageal smooth muscle contraction.[65,67] Nifedipine should, therefore, be the drug of choice, but diltiazem is a valuable alternative treatment because it produces fewer adverse effects (vasodilatation, headache, flushing) and is, therefore, better tolerated by patients.[15] However, calcium antagonists do not restore normal peristaltic function in oesophageal disorders.

Despite the promising pharmacological effects of calcium antagonists on oesophageal contraction amplitudes, there was no or only marginal clinical improvement in patients with hypercontractile oe-

Table III. Prospective clinical studies of botulinum toxin injection therapy in patients with diffuse oesophageal spasm

Investigator	No. of patients	Dose [units] (toxin used)	Responder (%)	Long term responder (%)[a]
Cassidy et al.[59]	10	80 (Botox®)	70	38
Nebendahl et al.[60]	3	100 (Botox®)	100	
Nebendahl et al.[61]	9	250 (Dysport®)	100	100
Storr et al.[14]	9	100 (Botox®)	89	89

a Includes those receiving multiple injections.

sophageal motility disorders when tested in double-blinded, placebo-controlled studies which also included patients with nutcracker oesophagus.[68] Furthermore, nifedipine has been shown to have no action on the contractility of the proximal third of the oesophagus and, therefore, should not be used in hypercontractile disorders of this section.[69] In general, these studies demonstrated that the chest pain associated with these disorders is probably not caused by the high contraction amplitudes as lowering the contractile response only marginally influenced the clinical scores.

3.3 Botulinum Toxin

Botulinum-toxin is a extremely potent bacteroid poison, which interacts selectively with cholinergic neurons to inhibit the release of acetylcholine at the presynaptic terminals.[70] Botulinum toxin rapidly and strongly binds to presynaptic cholinergic nerve terminals, is internalised and inhibits the acetylcholine release by interaction with a synaptosomal protein (SNAP-25).[70] Therefore, botulinum toxin shifts the balance of excitatory and inhibitory neurotransmitter influences towards the inhibitory side, a desired effect in spastic motility disorders.

Local injection of botulinum toxin has been suggested as a possible therapy for several spastic disorders of the gastrointestinal tract and to date is used with good clinical benefit in achalasia and chronic anal fissures.[71,72] Botulinum toxin injection showed no severe adverse effects and proved equally effective when compared with other interventional or operative treatment alternatives. The use of botulinum toxin has added a new therapeutic concept with few adverse effects to the interventional methods in spastic motility disorders.

Since 1995 when Pasricha published a double-blind, placebo-controlled study in 21 patients with achalasia, botulinum toxin injection is an accepted alternative therapy in achalasia with results comparable to pneumatic balloon dilatation.[73-75] Pasricha demonstrated an initial good result in 90% and an overall long term response (more than 6 months) in two-thirds of the patients, although 42% of the initial responders had to be reinjected.[73,74] Similar results could also be demonstrated in patients with achalasia by other authors.[75,76]

Botulinum toxin has recently been investigated in oesophageal motility disorders other than achalasia, such as diffuse oesophageal spasm and hypertensive lower oesophageal sphincter, with promising results in single cases and smaller patient selections but double-blind, placebo-controlled trials have still to be carried out (table III).[70,77] In a prospective study of botulinum toxin injections in 15 patients with nonachalasia oesophageal motility disorders unresponsive to medical therapy, including 5 patients with diffuse oesophageal spasm with lower oesophageal sphincter dysfunction, Miller et al.[7] demonstrated a good result in symptom score in 73% of patients after 1 month, although 67% of patients needed further treatment (botulinum toxin, pneumatic dilatation, bouginage) in long term (6 months) follow up. In 9 patients with manometrically proven diffuse oesophageal spasm, Storr et al.[14] injected botulinum toxin into the tubular oesophagus in 1.5cm steps. Responders were considers those with a 50% or greater decrease in pre- and post-treatment symptom score of dysphagia, chest pain and regurgitation. When these criteria were used, 30 days after injection, 89% of these patients had responded and were still in remission after 6 months.[14] Similar results have been reported by others.[59] In 3 patients with diffuse oesophageal spasm, Nebendahl et al.[60] injected botulinum toxin in 4 quadrants in 5 levels of the oesophagus and all patients had a marked improvement in symptom score, including resolution of chest pain. However, larger randomised, placebo-controlled trials on botulinum toxin therapy in patients with diffuse oesophageal spasm have not been carried out.

The dose required in diffuse oesophageal spasm is much lower than the doses required for systemic effect; however, medication with certain drugs (aminoglycosides) and certain disorders (myasthenia gravis) can increase the susceptibility of botulinum toxin.

Some drawbacks do have to be addressed. The pharmacological effect of botulinum toxin wears

off after a limited time period of about 6 months because of the formation of antibodies against botulinum toxin, and it has been suspected of causing scarring and fibrosis of the tissue injected.[70] This means that botulinum toxin injections have to be repeated and it is not known how many injections are needed to obtain a permanent effect (if ever).

3.4 Psychotropic Drugs

There is empirical and clinical evidence that sedatives, tranquilisers (particularly diazepam) and antidepressants might be effective in patients with symptomatic oesophageal motility disorders. Acute psychological stress has been shown to cause alterations of oesophageal motility such as an increase of upper oesophageal sphincter pressure and an increase of oesophageal body contraction amplitudes.[78,79] Comparing patients with recurrent chest pain and those with irritable bowl syndrome has demonstrated that patients with chest pain differ significantly in the degree of gastrointestinal susceptibility and somatic anxiety and their reaction to psychological stress.[80] Therefore, psychological testing might be helpful to determine the subgroup of patients that may benefit from psychotropic drugs or behaviour modification.

In a placebo-controlled, double-blinded study, Clouse and co-workers[57] demonstrated that a low dose of trazodone 100 to 150 mg/day can be beneficial in patients with oesophageal motility disorders. The antidepressant reduced the symptoms associated with the abnormal oesophageal motility; however, it had no significant influence on the oesophageal motility itself. This study was not focused on dysphagia and it is questionable whether chest pain and dysphagia can be compared in this way.[57]

4. Other Treatment

4.1 Behavioural Therapy, Biofeedback and Transcutaneous Nerve Stimulation

The usefulness of psychotropic drugs suggested that behavioral modification programmes and biofeedback might also be beneficial in the long term management of patients with diffuse oesophageal spasm. However, no controlled studies have been carried out so far.[81,82] In 8 patients with non-cardiac chest pain, it was demonstrated that the amplitude of oesophageal contractions can be controlled voluntarily, suggesting that patients with non-cardiac chest pain may benefit from biofeedback training.[83] There are some reports that transcutaneous nerve stimulation (TENS) might be effective in patients with oesophageal motility disorders to reduce the clinical symptoms in these patients.[84,85] TENS is further useful in patients with non-cardiac chest pain in reducing the oesophageal pain susceptibility, as evaluated by an intraoesophageal balloon distension test, and thus symptoms. TENS has been shown to be potent in reducing the propagation velocity but it does not affect the amplitude and duration of the contraction.[86]

4.2 Bouginage and Pneumatic Dilatation

Bouginage and pneumatic dilatation are therapeutical options for patients not responding to pharmacological treatment and seem to be useful in patients who have either elevated lower oesophageal sphincter pressure or incomplete lower oesophageal sphincter relaxations in association with diffuse oesophageal spasm.[87,88] Bouginage generally gives relief of dysphagia. Failure of bouginage should be followed by pneumatic balloon dilatation.[41] Pneumatic balloon dilatation is beneficial in 40% of patients with severe diffuse oesophageal spasm and up to 90% of patients with diffuse oesophageal spasm combined with lower oesophageal sphincter dysfunction but it has the risk of oesophageal perforation, haematemesis or fever.[1,89-91]

4.3 Surgical Treatment

Diffuse oesophageal spasm should primarily be treated conservatively and surgery should be confined only to patients who are severely symptomatic. If symptoms are otherwise intractable, extended myotomy is recommended by many surgeons, especially in those patients in whom muscular hypertrophy of the oesophageal wall is found.[92] Views differ concerning the extent of the myotomy,

whether the lower oesophageal sphincter should always be dissected as well and whether an antireflux procedure should be included.[62,92] Throughout the literature the success rates of surgical therapy range from 40 to 100% and an overall success rate of 75% can be observed when all publications are analysed.[62,92,93]

5. Conclusion

Similar to other known spastic oesophageal motility disorders (achalasia, hypercontractile oesophagus), the pathophysiology of diffuse oesophageal spasm is still unknown. Because of the lack of pathophysiological knowledge, there is a lack of pharmacological options to treat an underlying disorder. Nitrates, calcium antagonists and cholinergic agents are used for symptomatic treatment with varying results. Recently, botulinum toxin has been introduced into the treatment of diffuse oesophageal spasm with promising results but larger randomised, placebo-controlled studies are still required. In case of failure of pharmacological treatment modalities, then bouginage, pneumatic balloon dilatation and surgical myotomy can be offered to patients as therapeutic options.

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