Sildenafil in Esophageal Motility Disorders

Access:
professional
Article type:
drug information
Sildenafil in Esophageal Motility Disorders – Hard to Swallow?

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Introduction:
The two major functions of the esophagus are the transport of swallowed food to the stomach, and the prevention of retrograde flow of gastrointestinal contents.(1) After swallowing, the transport of food is achieved by coordinated, sequential peristaltic contractions along the length of the esophagus.(1) The two esophageal sphincters, which are zones of high intraluminal pressure, remain contracted between swallows and prevent retrograde flow. Patients complaining of difficulties in swallowing both solids and liquids, possibly accompanied by chest pain and regurgitation, may have an esophageal motility disorder.

Complex coordinated processes ensure that a food bolus is propelled in the proper direction. The upper esophageal sphincter (UES) and upper one-third of the esophagus are composed of skeletal muscle, whereas smooth muscle comprises the lower two-thirds of the esophagus and lower esophageal sphincter (LES). The UES is innervated by excitatory neurons only.(1) In contrast, the esophageal body and LES are regulated by both excitatory (contracting) and inhibitory (relaxing) input. The excitatory neurotransmitters are acetylcholine primarily, and substance P. Nitric oxide (NO) is the principle inhibitory neurotransmitter, with contributions also from vasoactive intestinal peptide. Inhibitory innervation is greater in the distal esophagus than the proximal esophagus.

Loss of NO inhibitory innervation and unopposed cholinergic excitatory activity underlies the pathology of several primary motility disorders. Disorders can be explained by defects in inhibitory or excitatory innervation. In primary esophageal motility disorders dysfunction is defined by standardized testing using manometry which measures pressure changes in different sites in the esophagus.(2,3) Achalasia is a disorder characterized by high LES pressure and nonperistaltic contractions causing dysphagia, chest pain and regurgitation in the patient. In diffuse esophageal spasm, contractions are of high amplitude and are poorly coordinated so that peristalsis is intermittent; patients complain of chest pain and dysphagia.

Patients with nutcracker esophagus exhibit hypercontraction of the distal esophagus but peristalsis still occurs; patients have chest pain but dysphagia is uncommon. Other less common motility disorders include hypertensive LES, hypocontracting esophagus, and hypotensive LES.

Pharmacological interventions have met with varying success.(1,2) Treatment of hypocontracting esophagus is primarily directed at controlling acid reflux. Therapy for abnormal peristalsis has targetted relaxation of esophageal and LES smooth muscle. Most clinical trials to date typically involved only small numbers of patients and efficacy has not been clearly established. Anticholinergics are usually of limited value.(4) Agents that relax smooth muscle, such as sublingual nitroglycerin, isosorbide dinitrate, or calcium channel blockers may be helpful in theory.(2,4) Chemical denervaton of cholinergic nerves in the distal esophagus can be achieved with botulinum toxin.(1,3) The antidepressants trazodone and imipramine have been shown to be effective in relieving chest pain in patients with esophageal motility abnormalities.(2) It is suggested that they may modify visceral sensory perception, rather than specifically treating the motility dysfunction.(2,3)

The most effective therapies have been difficult to define, due to the different pathophysiological mechanisms involved and difficulty finding a relationship between motility findings in the laboratory and symptoms experienced by patients.(3) Recently it has been speculated that phosphodiesterase type 5 (PDE5) inhibitors, specifically sildenafil, may be helpful in treating some esophageal motility disorders.

Mechanism:
Nitric oxide (NO) is a major inhibitory neurotransmitter in the gastrointestinal tract.(1,3) It stimulates production of intracellular cyclic guanosine monophosphate (cGMP), resulting in smooth muscle relaxation. By inhibiting the breakdown of cGMP by PDE5, sildenafil prolongs cGMP smooth muscle relaxing activity. It is hypothesized that sildenafil decreases LES, prolongs swallow-induced relaxation, and diminishes the amplitude of peristaltic pressure waves in smooth muscle of the esophagus.(5)

Clinical Trials:
Bortolotti et al. randomly assigned 14 patients with idiopathic achalasia to receive either sildenafil 50 mg or placebo, then measured LES tone, and pressure wave amplitude and propagation over a 60-minute period.(6) Sildenafil decreased the LES tone and residual pressure and lowered pressure wave amplitude compared to placebo, but statistically significant differences were observed for less than 45 minutes after drug administration. Headache was reported in one subject. Small study size, the failure to measure responses to solid foods or liquids, no description of clinical symptoms, and interpatient variability limit the applicability of this data.

In another study by the same authors, 14 patients with symptomatic hypertensive LES were randomly selected to receive either sildenafil 50 mg or placebo, and had esophageal motility and LES tone measured for 60 minutes.(7) LES tone and esophageal wave amplitude in the sildenafil group showed a decrease when compared against baseline and placebo, with the greatest differences noted approximately 10 minutes after drug administration. Differences were found to be statistically significant up to 60 minutes following drug administration. Patient symptoms were not reported.

Eherer, et. al. randomized 6 healthy subjects to either sildenafil 50 mg or placebo then

measured LES and esophageal motility.(8) Four subjects underwent ambulatory manometric measurements for 12 hours. Sildenafil significantly reduced LES pressure and amplitudes. In 3 of 4 subjects, the inhibitory effect lasted 8 hours, although statistical analysis was not performed in this phase of the trial. Subsequently in an open design, 11 patients with achalasia, hypertensive LES, nutcracker esophagus or esophageal spasm were given sildenafil 50 mg once daily to control their symptoms. Nine patients showed manometric improvement, but only 4 had symptomatic improvement. Two of those 4 did not wish to continue treatment due to side effects. Two patients had improvement of symptoms not limited by side effects; one with nutcracker esophagus receiving 50 mg daily, and one with hypertensive LES who received 25 mg per day. None of the patients with achalasia showed symptom improvement.

In 9 symptomatic patients with esophageal manometric findings indicative of nutcracker esophagus, 0.8 mg/kg sildenafil in solution or water was administered in a cross-over design.(9) Sildenafil decreased the resting LES pressure within 7.5 minutes of its administration, but the effect was statistically significant only from 7.5 – 30 minutes. The duration of LOS relaxation was only significantly reduced at 30 minutes. Similar results were observed for amplitudes of peristaltic pressure, although propagation velocity was not affected. Although results suggest sildenafil may be effective in lowering LES resting pressure and amplitude of distal esophageal peristaltic pressure waves, clinical efficacy was not assessed.

Conclusion:
By blocking the degradation of cGMP, sildenafil potentiates NO mediated relaxation of smooth muscle. Sildenafil lowers LES pressure and propulsive forces in the esophagus of healthy subjects, as well as patients with nutcracker esophagus, hypertensive LES and achalasia, but although the majority of patients demonstrate a good manometric response clinical improvement has not been satisfactorily demonstrated.(8) Speculation on the value of sildenafil is based solely on surrogate markers (manometric measurements). There are no studies demonstrating the clinical efficacy of sildenafil in esophageal motility disorders and side effects may be a limiting factor. While intriguing, further investigation is required to determine whether there is any role for PDE5 inhibitors in the treatment of these abnormalities.

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Originally published in BCPhA Tablet. 2005;14(6):5.
Keywords: sildenafil
esophageal achalasia
esophageal motility disorders

We are grateful to all the First Nations who have cared for and nurtured the lands and waters around us for all time, including the x?m??k??y??m (Musqueam), Sk?wx?wu?7mesh U?xwumixw (Squamish Nation), and s?l?ílw?ta? (Tsleil-Waututh Nation) on whose unceded and ancestral territory our centre is located.