Medical Management of Achalasia

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Achalasia is a primary esophageal motility disorder. Achalasia is characterized by the failure of the lower esophageal sphincter (LES) to relax normally when a food bolus is propelled down the esophagus. Long-standing failure of LES relaxation leads to disordered esophageal peristalsis and esophageal dilation. Patients present with progressive dysphagia, first to solid and then progressing to even liquid food. Chest pain, regurgitation, and sensation of heartburn can also be present. The disease is rare, affecting between 1 and 3 in 100,000 new patients annually. The prevalence of achalasia is estimated near 1 in 10,000 patients. The incidence in men and women is similar; there is no racial group that is more frequently affected than another; and diagnosis is typically made between the third and sixth decade of life [1, 2].

The failure of the LES to relax is due to the near total or total loss of the normal myenteric plexus ganglion cells in the distal esophagus [3]. Evidence suggests that this loss is due in large part to an autoimmune process [4], but there may also be a hereditary or infectious component [2]. Additionally, patients with achalasia seem to have abnormal nitric oxide signaling or production, leading to failure of LES relaxation [1, 5].

All treatment modalities for achalasia are palliative, and none can reverse the underlying abnormalities. Medical management of achalasia specifically aims to decrease LES tone to allow esophageal emptying with gravity and thereby relieving the bothersome symptoms of achalasia. The classes of medications most frequently used are calcium channel blockers and nitrates. Aside from these major classes of medications, a variety of other smooth muscle relaxants have been used in an effort to ameliorate achalasia, including anticholinergic and beta-adrenergic medications as well as selective and nonselective phosphodiesterase inhibitors.

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Calcium Channel Blockers

Calcium channel blockers act on calcium channels that are normally responsible for facilitating intracellular influx of calcium that is necessary for normal contraction to occur. Adverse effects include headaches, palpitations, headaches, and peripheral edema. Some gastrointestinal side effects, including nausea and vomiting, have also been described [6].

Nifedipine is the most well-studied calcium channel blocker employed in the treatment of achalasia. In numerous studies, including randomized controlled trials, nifedipine, at doses between 10 and 20 mg orally with meals, has been shown to decrease LES pressure by between 13% and 68% and improve symptoms by 53–80% [7, 8]. Effects occur between 10 and 30 min after administration and may last for up to 2 h [7].

With a relatively favorable side-effect profile when compared to nitrates, calcium channel blockers currently represent the mainstay of medical palliation of achalasia.

Nitrates

Nitrates are converted to nitric oxide after ingestion. They work by altering cyclic guanosine monophosphate (cGMP). Increased cGMP in turn decreases intracellular calcium, which contributes to smooth muscle relaxation. Adverse effects include headaches and hypotension [6].

Isosorbide dinitrate has not been evaluated in randomized trials, but studies show that its use can decrease LES pressure by 49–66% and improve symptoms by 58–87%. The typical dose is 5 mg orally with meals. Improved esophageal emptying has also been demonstrated [7, 8]. The onset of action is within 15 min and lasts between 60 and 90 min [7]. Even though nitrates are more efficacious than calcium channel blockers, their side effects are less well tolerated. Furthermore, tolerance may develop, limiting the usefulness of nitrates in management of achalasia.

Phosphodiesterase Inhibitors

Phosphodiesterase inhibitors (PDE) prevent the degradation of intracellular cyclic adenosine monophosphate (cAMP) and cGMP. As stated, this decreases intracellular calcium stores, promoting relaxation. Specific phosphodiesterase inhibitors that target the isoform 5-phosphodiesterase (PDE-5) specifically prevent changes specifically in cGMP. Concurrent use of nitrates and phosphodiesterase inhibitors potentiates the relaxing effects of these medications. Adverse effects include hypotension. If used with nitrates, hypotension can be profound and potentially life-threatening [6].

One study of the nonselective PDE aminophylline showed a decrease in LES pressure within 10 min of administration. The authors did not report a mean decrease

in pressure but did report that if pressure decreased by more than 25%, which occurred in 4 of 15 patients, the mean decrease in pressure was around 45%. Esophageal emptying was unchanged [9].

More recently attention has been turned to more selective PDEs, specifically the PDE-5 sildenafil. Administration of 50 mg sildenafil decreased LES tone, residual pressure, and also esophageal contractions. LES tone decreased by roughly 50%. The effect was reached within 10–15 min and lasted for less than 1 h. Symptoms were not monitored [10].

At this time not enough is known about PDEs' effect on achalasia to recommend their use over that of calcium channel blockers.

Anticholinergics

Anticholinergic drugs selectively block the nicotinic or muscarinic acetylcholine receptors. Antimuscarinic anticholinergics, such as atropine, inhibit acetylcholine signaling, which results in smooth muscle relaxation, among other effects. These medications can act as cardio-stimulants and can cause tachycardia. Dry mouth, blurry vision, and flushing are other common side effects [11].

In nonrandomized trials, anticholinergics have been shown to have variable effects on the LES pressure. There is not enough data available to support their routine use over the previously mentioned alternatives [7, 8].

Beta-Adrenergics

Beta-adrenergic medications act directly on the beta adrenergic receptors to cause sympathomimetic effects. The beta-adrenergic medications of use in achalasia are specifically beta-2 agonists. Activation of these receptors results in relaxation of smooth muscle through cAMP signaling. Hypokalemia and tremors are among the described side effects [12].

The beta-adrenergic drug terbutaline was evaluated alongside aminophylline and showed slightly more efficacy in decreasing LES pressure, achieving a greater than 25% decrease in 8 of 15 patients with a mean decrease in that group of 43%. Likewise, esophageal emptying was improved. The effects were seen within 10–20 min of administration and lasted for around 1 h [9].

In the absence of more data, as with anticholinergics, routine use over calcium channel blockers should not be recommended.

Summary

Several drug classes have been shown to be efficacious in the palliation of achalasia, reducing LES pressure and improving symptoms. The best-studied and understood class are the calcium channel blockers. While nitrates are perhaps slightly more

efficacious, the more favorable side-effect profile of calcium channel blockers makes them first-line medical therapy. Overall, however, it remains true that medical therapy for achalasia have limited utility in the treatment algorithm for achalasia. They should be considered for patients with minimally symptomatic disease or those who cannot or will not tolerate an intervention. Additionally, medications can be used as a bridge to more definitive intervention [7, 13, 14].

References

1. Ates F, Vaezi MF. The pathogenesis and management of achalasia: current status and future directions. Gut Liver. 2015;9(4):449–63.
2. Krill JT, Naik RD, Vaezi MF. Clinical management of achalasia: current state of the art. Clin Exp Gastroenterol. 2016;9:71–82.
3. Goldblum JR, Whyte RI, Orringer MB, Appelman HD. Achalasia. A morphologic study of 42 resected specimens. Am J Surg Pathol. 1994;18(4):327–37.
4. Clark SB, Rice TW, Tubbs RR, Richter JE, Goldblum JR. The nature of the myenteric infiltrate in achalasia: an immunohistochemical analysis. Am J Surg Pathol. 2000;24(8):1153–8.
5. Mearin F, Mourelle M, Guarner F, Salas A, Riveros-Moreno V, Moncada S, et al. Patients with achalasia lack nitric oxide synthase in the gastro-oesophageal junction. Eur J Clin Investig. 1993;23(11):724–8.
6. O'Shaughnessy KM. Arterial hypertension, angina pectoris, myocardial infarction and heart failure. In: Clinical pharmacology [Internet]. 11th ed. Elsevier; 2012 [cited 20 Oct 2016]. Available from: https://www-clinicalkey-com.ezp-prod1.hul.harvard.edu/#!/content/book/3-s2.0-B978070204084900063X.
7. Vaezi MF, Richter JE. Current therapies for achalasia: comparison and efficacy. J Clin Gastroenterol. 1998;27(1):21–35.
8. Bassotti G, Annese V. Review article: pharmacological options in achalasia. Aliment Pharmacol Ther. 1999;13(11):1391–6.
9. Wong RK, Maydonovitch C, Garcia JE, Johnson LF, Castell DO. The effect of terbutaline sulfate, nitroglycerin, and aminophylline on lower esophageal sphincter pressure and radionuclide esophageal emptying in patients with achalasia. J Clin Gastroenterol. 1987;9(4):386–9.
10. Bortolotti M, Mari C, Lopilato C, Porrazzo G, Miglioli M. Effects of sildenafil on esophageal motility of patients with idiopathic achalasia. Gastroenterology. 2000;118(2):253–7.
11. O'Shaughnessy KM. Cholinergic and antimuscarinic (anticholinergic) mechanisms and drugs. In: Clinical pharmacology [Internet]. 11th ed. Elsevier; 2012 [cited 20 Oct 2016]. Available from: https://www-clinicalkey-com.ezp-prod1.hul.harvard.edu/#!/content/book/3-s2.0-B9780702040849000616.
12. O'Shaughnessy KM. Adrenergic mechanisms and drugs. In: Clinical pharmacology [Internet]. 11th ed. Elsevier; 2012 [cited 20 Oct 2016]. Available from: https://www-clinicalkey-com.ezp-prod1.hul.harvard.edu/#!/content/book/3-s2.0-B9780702040849000628?scrollTo=%23hl0000196.
13. Lake JM, Wong RKH. Review article: the management of achalasia – a comparison of different treatment modalities. Aliment Pharmacol Ther. 2006;24(6):909–18.
14. Dughera L, Chiaverina M, Cacciotella L, Cisarò F. Management of achalasia. Clin Exp Gastroenterol. 2011;4:33–41.