Current and Prospective Pharmacotherapies in Gastroesophageal Reflux Disease

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Introduction

Gastroesophageal reflux disease (GERD) is very common and is a costly problem to manage. The annual direct cost for managing the disease is estimated to be more than $9 billion dollars in the USA.[1] In western populations, 25% of people over age 30 report having heartburn at least once a month, 12% at least once per week, and 5% describe daily symptoms.[2] However, the prevalence of the disease tends to be underestimated, with unrecognized GERD occurring in more than 50% of patients seen in general practice for unrelated conditions. GERD is defined as symptoms or mucosal damage produced by the abnormal reflux of gastric contents against the gradient of the lower esophageal sphincter (LES) pressure into the distal esophagus, leading to impaired quality of life and other complications.[3,4] The disease is thought to be caused by reduced pressure of the lower esophageal sphincter (LES) and delayed gastric emptying.[5] It is well-recognized that GERD is associated with a variety of clinical syndromes and that it is frequently a chronic condition, often requiring long-term maintenance therapy.[6] It can be subdivided into erosive esophagitis (EE) and non-erosive reflux disease (NERD). Patients with NERD have no mucosal breaks in the esophagus, but have typical reflux symptoms.[7] The spectrum of upper gastrointestinal complications of GERD includes erosive esophagitis, stricture and Barrett's esophagus, which may increase the risk of esophageal adenocarcinoma.[8,9] Treatment options available for GERD range from over-the-counter (OTC) antacids to proton pump inhibitors (PPIs) and anti-reflux endoscopic procedures and surgery. This article will review each of the pharmacotherapeutic options, including new developments in proton pump inhibitor isomers, potassium competitive acid blockers and endoscopic therapy for gastroesophageal reflux disease.

Antacids and Alginates

Self-medication with OTC antacids and acid suppressants is common, and many patients are unlikely to seek medical advice unless symptoms increase or persist. Liquid and tablet formulations of antacids and anti-reflux agents (such as alginic acid) are easily accessible to the public and are widely used as first-line treatments for reflux symptoms.

Mechanism of action and pharmacokinetics

Antacids, usually in aluminum- and/or magnesium-containing formulations, are weak bases that act locally to buffer the acidity of the gastric and esophageal contents, providing rapid, but relatively short-term symptom relief. They react with gastric acid to form water and a salt. Antacids also reduce peptic activity since pepsin is inactive at pH $>$ 4.0. Calcium-containing antacids (such as Tums and Rolaid) may be counterproductive since calcium salts stimulate gastrin secretion, which in turn stimulate gastric acid secretion.[10] Alginate-based raft-forming formulations have been marketed word-wide for over 30 years under various brand names, including Gaviscon. They are used for the symptomatic treatment

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of heartburn and esophagitis, and appear to act by a unique mechanism which differs from that of traditional antacids. In the presence of gastric acid, alginates precipitate, forming a gel. Alginate-based raft-forming formulations usually contain sodium or potassium bicarbonate and in the presence of gastric acid, the bicarbonate is converted to carbon dioxide which becomes entrapped within the gel precipitate, converting it into a foam which floats on the surface of the gastric contents, much like a raft on water.[11] The viscous, pH-neutral, protective barrier floats on the top of the gastric contents, preventing acid contact with the esophagus during an episode of reflux. Alginates are generally formulated in combination with an antacid. Raft formation occurs rapidly, often within a few seconds of dosing; hence alginate-containing antacids are comparable to traditional antacids for speed of onset of relief.

Clinical studies

Both antacids[12] and alginic acid[13,14] have been shown to be more effective than placebo in the relief of symptoms induced by a heartburn promoting meal. In addition, combined antacid/alginic acid therapy may be superior to antacids alone in the control of symptoms.[15,16] Antacids have also been shown to increase LES pressure and decrease gastroesophageal reflux.[17,18] Clinical studies suggest alginic acid is effective in the treatment of reflux disease, but probably no better than antacid therapy.[19–21] Cochrane systemic review comparing antacid/alginate therapy with H_2-receptor antagonist (H_2RA) therapy showed that acid suppression therapy is superior in both healing of erosive esophagitis and in symptom persistence compared with antacid/alginate therapy[22] and antacid/alginate therapy did not confer any statistically significant additional benefit over H_2RA therapy alone.

Safety

Antacids and alginic acid are generally safe. Magnesium-containing antacids can cause diarrhea; aluminum-containing antacids can causes constipation. Preparations that contain both of these agents aid in normalizing bowel function. Absorption of cations from antacids (Mg^{++}, Al^{++}, Ca^{++}) is usually not a problem in patient with normal renal function but can cause toxicity in patients with renal insufficiency. The sodium content of antacids can be an important consideration in patients with hypertension or congestive heart failure. Systemic absorption of sodium bicarbonate can produce transient metabolic alkalosis, thus this antacid is not recommended for long-term use. Concurrent administration of antacids and other medications is usually not advisable because of the effects of alteration of gastric and urinary pH by antacids can alter the rates of dissolution and absorption, bioavailability, and renal elimination of many drugs.

Efficacy

Although antacids and alginates may be useful in milder cases of GERD, OTC antacids provide effective symptom relief in only approximately 25% of patients with GERD.[23,24] Furthermore, these drugs have no efficacy in healing erosive esophagitis.[22,25]

Patient preference

The necessity of frequent dosing and the inconvenience of liquid dosage forms limit the usefulness of antacids and alginates.

Place in therapy

OTC antacids and alginates are easily accessible and are effective in control of mild to moderate symptoms of reflux disease and promoting healing of duodenal ulcers. Evidence for efficacy in treatment of acute gastric ulcer is less compelling.[10] These agents can also be useful as PRN therapy for breakthrough symptoms of pyrosis in patients who are already on daily PPI therapy. They are also useful in special populations, such as pregnant patients, where acid suppressive medications may not be the best option.

Conclusions

Antacids and alginates are OTC treatments for symptoms of reflux disease. Most patients will not respond adequately to these treatments and need further intervention.[7] When symptoms persist, or when continuous therapy is required, or if alarm symptoms or signs develop, the patient should have additional evaluation and treatment.[3] Objective reviews have shown that antacids/alginates are inferior to H2RAs or PPIs in healing of erosive esophagitis or in relieving of symptoms of GERD.

Histamine H_2-Receptor Antagonists

Gastric acid secretion by parietal cells of the gastric mucosa have a complex control mechanism. Acetylcholine, histamine, prostaglandins E_2 and I_2, and gastrin are all involved. Histamine H_2-recptor antagonists (H_2RAs) work by blocking histamine from binding to the parietal cell histamine H_2-receptors, thereby inhibiting gastric acid secretion. All four of the H_2RAs (cimetidine, ranitidine, famotidine and nizatidine) approved for use in the United States are available OTC usually at a dose half that of the standard prescription dose and have been shown to decrease gastric acid, particularly after a meal.[3] These are approved for acute treatment of episodic heartburn, or for prophylaxis before consumption of food or drink expected to trigger reflux symptoms. Many patients can predict when they are going to suffer from reflux and can premedicate with the OTC H_2RAs. While there are differences in potency, duration, and rapidity of action, they may be generally used interchangeably.

Mechanism of action and pharmacokinetics

H_2RAs inhibit acid secretion by competitively and reversibly blocking parietal cell H_2-receptors, one of the stimulants to acid production.[26] Blockage of the binding of histamine to H_2 receptors leads to reduction of intracellular concentrations of cyclic AMP and thereby, secretion of gastric acid. These agents completely inhibit gastric acid secretion induced by histamine or gastrin. The H_2RAs have a slower onset of action than the antacids, and suppress gastric acid for 4–10 hours. Due to this, most H_2RAs are prescribed twice daily. H2RAs are given orally with rapid absorption, and distribute widely throughout the body, including in breast milk and across the placenta, and are excreted mainly in the urine.[10] Peak plasma concentrations are attained from 1 to 3 hours after an oral administration. Plasma concentrations of H2RAs and inhibition of gastric acid secretion are directly related, implying a rapid equilibration between drug concentration in plasma and at the site of action.[27] Cimetidine, ranitidine, and famotidine are metabolized by the cytochrome P450 enzymes (CYP2C19 and CYP3A4) in the liver; nizatidine is eliminated principally by the kidney.

Clinical Studies

A Cochrane systemic review has been completed on the efficacy of H_2RAs in healing esophagitis or resolving reflux symptoms or both.[22] This review identified 10 randomized control trials (RCTs) involving 1241 patients that compared H_2RAs with placebo at 6 weeks. Overall, esophagitis persistence in the group taking H_2RAs was 59.0% compared to 79.7% in the placebo group. There was statistically significant benefit of taking H_2RAs compared to placebo in healing of esophagitis (RR 0.74, 95% CI = 0.66 to 0.84) with a number needed to treat (NNT) of five (95% CI = 3–7). Symptom persistence in the group taking H_2RA therapy was 57.7% compared to 83.7% in the placebo group. There was also statistically significant benefit of taking H_2RA compared to placebo in symptom relief (RR 0.67, 95% CI = 0.48 to 0.95) with a NNT of 5 (95% CI = 2–17).

The effects of different dosing strategies in H_2RA therapy were also evaluated in the same review. Nine RCTs compared standard dose to high or split-doses of H_2RAs involving 1564 patients over four to eight weeks. Overall, esophagitis persistence in the group taking standard dose H_2RA was 40.0%, compared to 40.0% in the high or split-dose group. There was no statistically significant benefit of taking high or split-doses of H_2RAs in healing of esophagitis (RR 1.0, 95% CI = 0.90 to 1.12). Five RCTs evaluated global symptom persistence between groups taking standard dose versus high or split-doses H_2RAs, involving 720 patients over 6 to 12 weeks. There was no statistically significant benefit of taking high or split-doses of H_2RAs compared to standard dose in symptom relief (RR 1.16, 95% CI = 0.84 to 1.60).

H_2RA therapy was also compared to prokinetics or mucosal protecting agents or antacid/ alginate in treating esophagitis, involving 200 patients over 6 weeks. There was no statistically significant benefit of taking prokinetic or mucosal protecting agent or antacid/alginate compared to H_2RA therapy in healing esophagitis or in symptom relief. H_2RAs alone versus H_2RAs plus prokinetics or mucosal protecting agents was also evaluated in small RCTs, involving 88 patients over 12 weeks with no statistically significant benefit of additional therapy with prokinetics or mucosal protecting agents.[22]

Safety

H_2RA therapy is generally safe as compared to placebo in the Cochrane systemic review.[22] 39.8% patients in H_2RA group reported at least one adverse

event compared to 36.4% in placebo group. There showed no statistically significant harm of taking H_2RA therapy compared to placebo (RR 1.10, 95% CI = 0.88 to 1.38), or in taking high or split-dose H_2RA therapy compared to standard dose (RR at standard dose arm 0.55, 95% CI = 0.19 to 1.59), or in taking H_2RAs plus prokinetic or mucosal protecting agent compared to H_2RA therapy alone (RR at H_2RA alone arm 0.79, 95% CI = 0.58 to 1.08) in producing adverse events. Most commonly reported adverse events were diarrhea and headache. CNS symptoms (hallucinations and confusion) are more common in elderly patients. Cimetidine can cause gynecomastia, galactorrhea, and reduced sperm count, particularly with prolonged use. Cimetidine inhibits cytochrome P450 and can slow metabolism of several drugs (for example, warfarin, phenytoin, diazepam), thus sometimes resulting in serious adverse clinical effects.[10] Most H_2RAs cross the placenta, but teratogenic effects to the fetus have not been reported in animal studies. H_2RAs are classified as pregnancy category B and use with caution during pregnancy is advised.

Efficacy

All four agents are effective in promoting healing of duodenal and gastric ulcers. They are less effective in the treatment of esophagitis. Acid suppression, even with full-dose H_2RAs, is incomplete, resulting in approximately 70% inhibition over 24 hours.[27,28] These drugs are, therefore, less effective in term of acid control than PPIs, which have been shown to reduce acidity by up to 97%.[29] The rapid development of pharmacological tolerance (within 7–14 days) is a further disadvantage of H_2RAs, and the loss of gastric acid secretion suppression obtained with these agents may partially explain their unsatisfactory use in patients with GERD.[25]

Patient preference

All four H_2RAs are relatively well-tolerated, effective and easily accessible OTC.

Place in therapy

H_2RA therapy for acute, episodic reflux symptoms is safe and relatively effective. These drugs are useful in managing both gastric and duodenal ulcers and acute stress ulcers associated with major physical trauma in high-risk patients in intensive care units. H2RAs are also used in treatment for hypersecretion of gastric acid due to hypergastrinemia associated with gastrinoma (Zollinger-Ellison syndrome). However, the advent of proton pump inhibitors had decrease the use of H_2RAs in all settings. H_2RA medications are conveniently available both by prescription at standard therapeutic doses and OTC at usually half of standard doses. There is a role for H2RAs in adjunctive therapy for breakthrough symptoms in patients already on PPI therapy.

Conclusions

H_2RAs are safe and effective in controlling symptoms of acute reflux disease. It is important that patients visit their physician before using H_2RA medications beyond their 14-day indication since some will be at risk for erosive esophagitis, Barrett's esophagus or other upper gastrointestinal pathology and should be evaluated and, if appropriate, referred for endoscopic screening. Systemic review showed that H2RA therapy is superior to antacid/alginate therapy and is inferior to PPI therapy (see discussion in section of PPI therapy).

Mucosal Protective Agents

Introduction

Sucralfate, colloidal bismuth and misoprostol, known as cytoprotective compounds, have several actions that enhance mucosal protection mechanism, thereby preventing mucosal injury, reducing inflammation, and healing existing ulcers. Misoprostol, a synthetic analog of prostaglandin E_1, enhances mucosal resistance to injury via a mechanism different than that of sucralfate and bismuth.

Mechanism of action and pharmacokinetics

Sucralfate, a complex of aluminum hydroxide and sulfated sucrose, binds to positively charged groups in proteins of both normal and necrotic mucosa. By forming complex gels with mucus, sucralfate creates a physical barrier that impairs diffusion of HCl and prevents degradation of mucus by pepsin. It also stimulates prostaglandin release, mucus and bicarbonate output, and inhibits peptic digestion. These mechanisms lead to the healing of duodenal ulcers.[10] Because sucralfate requires an acidic pH for activation, it should not be administered with H_2 antagonists PPIs or antacids.

Colloidal bismuth effectively heals peptic ulcers. It inhibits the activity of pepsin, increases mucous secretion and interacts with proteins in necrotic mucosal tissue to coat and protect the ulcer crater. Bismuth subsalicylate exhibits both antisecretory and antimicrobial action. The salicylate moiety provides antisecretory effect and the bismuth exhibits antimicrobial directly against bacterial and viral gastrointestinal pathogens. Systemic absorption of the bismuth moiety is $<1\%$, and $>90\%$ for subsalicylate. Bismuth subsalicylate is converted to salicylic acid and insoluble bismuth salts in the GI tract.

Misoprostol not only inhibits the secretion of hydrochloric acid and pepsin in the stomach that can cause mucosal injury, but it also stimulates secretion of mucus and bicarbonate in the stomach and the small intestine that enhance mucosal resistance to injury. A deficiency in prostaglandins is thought to be involved in the pathogenesis of peptic ulcers.[10] Although misoprostol has cytoprotective actions, it is clinically effective only at higher doses that diminish gastric secretion.[10]

Clinical studies

Sucralfate provides similar level of symptomatic relief to that of H_2RAs; however, studies evaluating sucralfate in the healing of GERD have produced inconsistent results, with reported healing rates varying from 17%–67%.[30,31] A Cochrane systemic review evaluated the effectiveness in healing erosive esophagitis of mucosal protective agents compared with H2RA therapy alone or H2RAs combined with mucosal protective agents did not show statistically significant benefit of taking these mucosal protective agents alone or together with H2RA therapy.[22] The same review identified 3 RCTs evaluating 266 participants comparing mucosal protecting agent (sucralfate) versus antacid/alginate or placebo in healing of esophagitis at six weeks. There was no statistically significant benefit of taking mucosal protecting agent therapy compared to antacid or placebo in healing of esophagitis (RR of persistence at six weeks 0.82, 95% CI 0.67 to 1.01). One RCT evaluated 78 participants at six weeks and found no statistically significant benefit of taking mucosal protective agent therapy (sucralfate) compared to antacid in symptom relief (RR of symptom persistence at six weeks 0.81, 95% CI 0.65 to 1.01). Another RCT evaluated 63 participants with GERD taking mucosal protective agent alone (sucralfate monotherapy) versus sucralfate plus cimetidine.[32] There was no statistically significant benefit of the combination therapy compared to sucralfate monotherapy in healing of peptic reflux esophagitis (RR of persistence of esophagitis in sucralfate monotherapy arm 1.03, 95% CI 0.80 to 1.33).

Safety

Sucralfate is safe due to very limited systemic absorption. Bismuth subsalicylate is pregnancy category C/D. Bismuth subsalicylate should not be used in children with influenza or chickenpox because of risk of Reye's syndrome. Misoprostol has dose-related diarrhea and nausea as common side effects, limiting its usefulness. It can also cause uterine contraction and is strongly contraindicated in pregnancy.

Efficacy

The efficacy of mucosal protective agents in healing esophagitis has not been documented in systemic database review.

Patient preference

Palability, liquid formulations, and frequency of administration limit patient preference for both sucralfate and bismuth-containing compounds. This also effects compliance to therapy.

Place in therapy

Sucralfate is well-tolerated and can be used to promote mucosal healing in cases of gastric or duodenal ulcers. Misoprostol is routinely used prophylactically in patients who are taking NSAIDs who are at high risk of NSAID-induced ulcers, such as the elderly or patients with ulcer complications. It is unclear if its use can alter significant complications.

Conclusions

Mucosal protective agents are inferior to antacid/alginates, H2RAs and PPIs in the treatment of erosive esophagitis and in relieving symptoms of GERD. They have limited usefulness in the treatment of duodenal and gastric ulcers. Misoprostol previously had a role in prophylaxis of NSAID-induced ulcer; however, its use has been significantly diminished since the advent of PPIs.

Prokinetics and $GABA_B$ Receptor Antagonists

Defects in esophagogastric motility (LES incompetence, poor esophageal clearance, and delayed gastric emptying) are central to the pathogenesis of GERD.[33] If these defects could be corrected then GERD would be controlled. Promotility agents may be used in selected patients with GERD, especially as an adjunct to acid suppression. Prokinetic therapy increases LES pressure, enhances gastric emptying rate and peristalsis, thus reduces gastroesophageal reflux symptoms. A subset of patients with GERD with refractory symptoms during therapy with proton pump inhibitors (PPIs), have persistent non-acid duodeno-gastroesophageal reflux (duodenal reflux). In these patients, baclofen, the prototype $GABA_B$ receptor agonist, has been shown to reduce postprandial reflux of all types, both acid and non-acid, by inhibiting the transient lower esophageal sphincter relaxations (tLESRs).

Mechanism of action and pharmacokinetics

The prokinetic (gastrokinetic) agents (bethanacol, metoclopramide, domperidone and cisapride) stimulate gastrointestinal motility by acting on dopaminergic receptors in the gut and/or enhancing the release of acetylcholine by an agonist action on serotonin ($5\text{-}HT_4$) receptors. Dopamine is an important mediator of gastrointestinal secretion, absorption, and motility. Acetylcholine is synthesized in cholinergic neurons and is the principal positive regulator of gastrointestinal motility.[34]

Bethanechol is a direct-acting muscarinic receptor agent that acts by stimulating the parasympathetic nervous system to release acetylcholine. It has been shown to increase LES pressure and improve esophageal peristaltic clearing.[27] Bethanechol has variable systemic absorption, with onset of action between 30 to 90 minutes after oral ingestion, and duration of action up to 6 hours. It should be taken 1 hour before meals.

Metoclopramide is a dopaminergic antagonist that acts by increasing the lower esophageal sphincter pressure, aids in esophageal peristalsis and speeds gastric emptying.[35] Bioavailability after oral ingestion of metoclopramide is 65% to 95%, with time to peak serum concentration of 1 to 2 hours. Onset of action for oral administration is 0.5 to 1 hour; for intravenous administration is 1 to 3 minutes; and for intramuscular administration is 10 to 15 minutes. Duration of therapeutic action is 1 to 2 hours regardless of route of administration. It is excreted mainly in urine (85%).

Domperidone is another dopamine receptor blocker, but unlike metoclopramide does not easily cross the blood-brain barrier and therefore has little central nervous system effects. It has peripheral dopamine receptor blocking properties and increases esophageal peristalsis and LES pressure, increases gastric motility and peristalsis; therefore, facilitating gastric emptying and decreasing small bowel transit time.[36] It is rapidly absorbed following oral, intramuscular, and rectal administration. Although absorption from the GI tract is nearly complete, oral bioavailability is only 13%–17% because of extensive first-pass and gut-wall metabolism.[36] It is mainly metabolized by the liver via N-dealkylation and hydroxylation, with the half-life elimination of 7 hours. Time to peak serum concentration after an oral ingestion is 30 minutes. It is excreted in feces (66%) and in urine (31%).

Cisapride belongs to a subgroup of substitute benzamides and does not possess dopamine receptor-blocking or direct cholinergic receptor-stimulating properties.[37] It acts as a postganglionic serotonin $5\text{-}HT_4$ receptor agonist. The gastrointestinal tract contains more than 95% of the total body serotonin, and serotonin is important in a variety of processes, including epithelial secretion, bowel motility, nausea and emesis. Serotonin released from mucosal cells stimulates sensory neurons, initiating a peristaltic reflex and secretion via $5\text{-}HT_4$ receptors.[34] The mechanism of action of cisapride might, for the most part, be explained by an enhancement of the physiologic release of acetylcholine at the level of the myenteric plexus. Cisapride is absorbed rapidly with onset of action in 30 minutes to 1 hour after an oral administration. It is metabolized extensively by the liver to norcisapride. It has a half-life of 6 to 12 hours. It is excreted in small amounts ($<10\%$) in urine and feces.

GABA (γ-aminobutyric acid) is found primarily in the myenteric plexus and is involved in regulating smooth muscle contraction of the gastrointestinal tract. $GABA_B$ receptors are present in the nucleus tractus solitarius and in the dorsal motor nucleus of the vagus, which are known as centers that integrate the afferent preganglionic signal arising from gastric tension mechanoreceptors and the lower esophageal sphincter. It has been shown

that activation of GABA receptors with the $GABA_B$ agonist baclofen inhibits tLESRs, gastroesophageal reflux, and gastric secretion.[38,39] The absorption of baclofen following an oral administration is rapid, with time to peak serum concentration within 2 to 3 hours and onset of action in 3 to 4 days. It is metabolized by the liver in approximately 15% of dose, and excreted in urine and feces mainly as unchanged drug (85% of dose).

Clinical studies

Bethanechol 25 mg four times daily was compared to placebo in one small placebo-controlled study showing reduction in heartburn symptoms and antacid use after 2 months of therapy.[40] However, the improvement of GERD symptoms in patients receiving bechanechol plus antacids was not statistically significantly different from that in patients receiving antacid plus placebo.[41] Results also differ among studies examining the efficacy of bethanechol in healing erosive esophagitis. In a comparative trial of bethanechol and cimetidine, the two agents had fairly similar healing rates (52% of patients receiving bethanechol and 68% of those receiving cimetidine experienced complete healing). Both agents were administered with high doses of antacids, which may have helped produce these high healing rates.[40] Interestingly, although Thanik and colleagues[41] found bethanechol to be no more effective than placebo in improving GERD symptoms, 45.5% of patients receiving bethanechol 25 mg four times daily experienced complete healing of erosive esophagitis, compared with 13.6% of patients receiving placebo plus antacids ($P < 0.015$).

A Cochrane systemic review performed comparing metoclopramide to placebo in the treatment for GERD in children.[42] There were 7 RCTs, with only 4 of the RCTs studied the effect of metoclopramide for longer than 2 day period. Conflicting results were observed, but data suggests that metoclopramide may be superior to placebo in reflux index and daily symptoms in infants with GERD. In adults with GERD, small trials evaluated metoclopramide 10 mg four times daily, either taken alone or in combination with an antacid, both were more effective than placebo at improving symptoms.[43,44] Although symptom improvement has been demonstrated with metoclopramide, this agent does not seem to be significantly more effective than placebo at promoting healing of erosive esophagitis.[40] Comparative studies have found that metoclopramide is as effective as H_2RAs (cimetidine and ranitidine) in relieving heartburn and other GERD symptoms.[45,46] All of these comparative trials were conducted in small patient populations and all but one were conducted without a placebo control.

Pritchard et al[17] performed a meta-analysis of studies of domperidone used to treat gastroesophageal reflux disease in children.[47] The authors found only 4 valid RCTs, none of which provided any robust evidence of domperidone's efficacy. As with bethanechol and metoclopramide, data on the efficacy of domperidone in GERD treatment come from small studies. The efficacy of domperidone in GERD treatment has not been persuasively proven in well-controlled double-blind studies and results with domperidone at dosages of 20 mg three or four times daily are inconsistent. Other studies have shown domperidone to be effective in relieving symptoms but not in healing esophagitis.[40] A recent Cochrane database systemic review also showed no statistically significant benefit of taking prokinetic therapy compared to placebo in healing of esophagitis (RR 0.71, 95% CI 0.46 to 1.10).[22]

A Cochrane systemic review identified 3 RCTs evaluating 198 participants at 12 weeks for the effects of prokinetic therapy (cisapride) versus placebo in the treatment of reflux esophagitis.[22] Overall esophagitis persistence in the group taking Cisapride was 53.1%, compared to 67.6% in the group taking placebo. There was no statistically significant benefit of taking cisapride compared to placebo in healing of esophagitis. One RTC evaluated 322 participants at eight weeks for persistence of symptom (heartburn). Heartburn persistence in the group taking cisapride 20 mg BID was 75.5%, compared to 81.1% in the group taking placebo. There was no statistically significant benefit of taking cisapride therapy compared to placebo in heartburn relief.[48]

Baclofen has been shown to decrease acid and non-acid reflux through the inhibition of tLESRs, thus increases the LES pressure limiting reflux of the gastric content into the distal esophagus.[49,50] Vela and colleagues compared acid and non-acid reflux after placebo and baclofen using combined multichannel intraluminal impedance and pH (MII/pH). Baclofen was shown to reduce postprandial acid and non-acid reflux and their associated symptoms.[51] It was also shown to reduce

reflux episodes during the first three postprandial hours in patients with GERD and in normal controls.[52] The number of reflux episodes and per cent time with pH < 4 was significantly lower after baclofen in GERD patients and controls ($p < 0.003$; $p < 0.0007$). Four weeks after initial administration of baclofen, the number of reflux episodes and percentage of time with pH < 4 significantly decreased in all GERD patients ($p < 0.003$; $p < 0.02$). Symptom scores significantly improved after treatment with baclofen ($p < 0.0007$). Baclofen has also been reported to reduce both the number of reflux episodes and the percent time esophageal acid exposure (with pH < 4.0) after a single dose of 40 mg.[53]

Safety

Metoclopramide has a number of adverse effects including diarrhea, drowsiness, restlessness, gynecomastia, and galactorrhea. Patients taking metoclopramide can experience extrapyramidal reactions, including dystonia and tardive dysknesia. While the manufacturer of metoclopramide reports the incidence of extrapyramidal reactions as 1 in 500 patients, in clinical practice the incidence of these reactions appears to be substantially higher. In children, it may be as high as 15%.[54] There have also been isolated cases of metoclopramide induced methemoglobinemia.[55]

Baclofen is pregnancy category C and does enter breast milk in a small quantity. The agent also has many central nervous system side effects, such as drowsiness, nausea, and the lowering of the threshold for seizures.[56]

Post- marketing reports and pharmacokinetic and electrophysiological data provided evidence that cisapride is associated with the occurrence of QT prolongation and torsades de pointes. The risk of fatal arrhythmia with cisapride was believed to outweigh the benefit for the approved indication, treatment of nocturnal heartburn due to gastroesophageal reflux disease, leading to the drug's discontinuation in the United States in 2001.[57]

Bechanechol, at the dosage level necessary to treat GERD (25 mg four times daily), can cause significant side effects, such as abdominal cramping, blurred vision, fatigue, and increased urinary frequency. Side effects occur in about 10% to 15% of patients, and are more common in the elderly. Bethanechol is also contraindicated in patients with cardiac conduction defects and coronary artery disease, hyperthyroidism, bronchial asthma and those with mechanical obstruction of the gastrointestinal or lower urinary tract.[54]

Since the withdrawal of cisapride from the market due to its side effects profile, domperidone was becoming the preferred prokinetic agent in Europe. The drug has never been approved for use in the United States. Domperidone's effect on cardiac repolarization involves the same mechanism as for cisapride and other medications known to prolong the QT interval. There are reported cases of QT prolongation in infants taking oral domperidone for GERD, but none of the cases studied had malignant arrhythmias.[58] Another significant side effect of domperidone is hyperprolactinemia which occurs in 10% to 15% of patients.[3]

Efficacy

Overall, Cochrane database systemic review of medical treatments for maintenance therapy of GERD in adults found that prokinetics showed some benefit over placebo;[59] however, prokinetic therapy has not been showed to heal esophagitis in patients with GERD.[22]

Patient preference

Poor patient preference due to significant side effects profile and lack of significant improvement of reflux symptoms limits their usefulness.

Place in therapy

Significant side effects and marginal efficacy have limited the therapeutic use of prokinetics as monotherapy in GERD. Baclofen and domperidone has limited role as adjunctive therapy in patients with NERD while on PPI therapy. A guideline on GERD management developed by the American Gastroenterological Association Institute recommends against use of metoclopramide as monotherapy or adjunctive therapy because of its side effects.[60]

Conclusions

Prokinetic drugs can theoretically be useful adjuncts in the treatment of GERD by increasing the LES pressure, enhancing gastric emptying, or improving peristalsis. Clinically, however, these drugs are marginally useful. The currently available promotility agents are also hampered by their side effects profile.

Proton Pump Inhibitors

As a drug class, proton pump inhibitors (PPIs) are the most effective pharmacologic agents for the treatment of GERD.[3] There are currently 5 PPIs available in the United States: omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole. Only omeprazole is available as an OTC medication.

Mechanism of action and pharmacokinetics

PPIs bind to the H^+/K^+-ATPase enzyme system (proton pump) of the parietal cell, suppressing secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid. At standard doses, PPIs inhibit more than 90% of the basal and stimulated gastric acid secretion. Acid suppression begins within 1 to 2 hours after the first dose of PPIs. All PPIs are enteric-coated pro-drug to protect them from premature activation by gastric acid. After absorption in the duodenum, they are transported to the gastric acid parietal cell canaliculus, where they are converted to active species. Metabolites of these agents are excreted in urine and feces.[10] All PPIs are metabolized in the liver via the cytochrome P450 system, specifically by the CYP2C19 and CYP3A4 enzymes.[27]

Clinical studies

Although several studies have been performed in which multiple PPIs have been compared head-to-head, only one study has evaluated all marketed PPIs in a 5-way crossover design at doses approved by the US Food and Drug Administration (FDA) for the treatment of erosive esophagitis.[61] This randomized study evaluated 34 H. pylori—negative patients with heartburn more than 3 times a week. Each of the 5 treatments was 5 days in duration, with intragastric pH measured on day 5. A washout period of 7 to 10 days was required between treatments, with doses administered in the treatment center and the pH study performed in this controlled environment as well. Esomeprazole 40 mg demonstrated a statistically significant superiority compared with the other 4 PPIs in the mean time intragastric pH above 4.0. It has been shown that when intragastric pH is raised above 4, pepsin activity is sufficiently reduced so that injury and symptoms are extremely rare.[62] Four other 2-way crossover, RCTs reported clinical pharmacology studies in patients with symptoms of GERD.[63] Esomeprazole 40 mg maintained intragastric pH greater than 4 for a significantly higher mean percentage of the 24-hour period compared with all other PPIs on Day 1 (esomeprazole 40.6% vs. lansoprazole 33.4%, $P = 0.0182$; esomeprazole 50.3% vs. pantoprazole 29.1%, $P < 0.001$; esomeprazole 41.0% vs. rabeprazole 29.4%, $P = 0.002$) and on Day 5 (esomeprazole 57.7% vs. lansoprazole 44.5%, $P < 0.0001$; esomeprazole 69.8% vs. omeprazole 43.7%, $P < 0.0001$; esomeprazole 67.0% vs. pantoprazole 44.8%, $P < 0.0001$; esomeprazole 59.4% vs. rabeprazole 44.5%, $P < 0.0001$). Conversely, another randomized 2-way crossover study revealed that rabeprazole 20 mg had a significantly greater effect on nighttime (10 pm to 8 am) acid suppression than esomeprazole 40 mg for both mean percentage of time intragastric pH was greater than 3 ($P = 0.005$) and greater than 4 ($P = 0.001$).[64]

In evaluating the effectiveness in healing erosive esophagitis among PPIs, the available data reflect equivalency between lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg, and rabeprazole 20 mg when any two are compared head to head in a RCT.[65] The largest healing studies have been performed to compare healing of erosive esophagitis between esomeprazole 40 mg and lansoprazole 30 mg ($N = 5,241$),[66] omeprazole 20 mg ($N = 3,729$),[67,68] and pantoprazole 40 mg[69] ($N = 3,161$). The overall healing rates of erosive esophagitis for once-daily PPI therapy range from 84% to 95%, reinforcing the overall excellent clinical outcomes with all PPIs. Overall, esomeprazole 40 mg demonstrates a significant 3%–10% increase in healing rates at 8 weeks versus the comparator PPIs.[6] Meta-analysis of six randomized, 2-way crossover trials evaluating 13,572 patients confirmed that esomeprazole 40 mg once daily provided significantly higher healing rates of erosive esophagitis at 4 weeks (RR 0.92, 95% CI 0.90–0.94, $P < .00001$) and at 8 weeks (RR 0.95, 95% CI 0.94–0.97, $P < 0.00001$) when compared with the other PPIs.[70]

Examination of the healing rated by Los Angeles grade underscores the potential relationship between pH control and clinical efficacy. The magnitude of benefit that esomeprazole 40 mg provides over the standard-dose PPIs increases with the severity of the underlying erosive esophagitis, becoming statistically significant ($P < 0.00001$)

for grade B, C, and D.[70] This reinforces the argument that when reflux esophagitis is more severe, greater acid inhibition will result in superior clinical outcomes.

Patients with reflux esophagitis often require long-term maintenance therapy. The majority of the head-to-head clinical trials reflect no difference in maintenance of healing of erosive esophagitis at either 6 months, 1 year, or 5 years.[6] Overall, 85%–90% of patients evaluated remained healed, reemphasizing the long-term efficacy of PPIs.

Appropriate dosing of PPI maintenance regimens may be an important consideration in clinical practice. Lauritsen and colleagues compared 6 months of therapy with esomeprazole 20 mg to lansoprazole 15 mg, the FDA-approved doses for maintenance of healing of erosive esophagitis.[71] Erosive esophagitis was initially healed with esomeprazole 40 mg. The 6-month remission rates were lower than those reported in 4- and 8-week healing trials using higher-dose PPI. This suggests that when acid control is decreased, as might occur with lower maintenance doses, there may be a fall-off in control of disease, especially in more severe presentations.

Another study had evaluated the efficacy of daily PPI therapy (esomeprazole 20 mg QD) versus on-demand PPI therapy (esomeprazole 20 mg PRN) for maintenance of healed erosive esophagitis over 6 months.[72] Erosive esophagitis was previously treated with a 8-week course of esomeprazole 40 mg once daily. Significantly more patients treated with continuous daily therapy achieved remission at 6 months compared with those in the on-demand group. This study demonstrates that mucosal integrity cannot be assured by on-demand PPI maintenance therapy in patients with erosive esophagitis.

Safety

Long-term use of PPIs has potential areas of concern including carcinoid formation, development of gastric adenocarcinoma (especially in patients with Helicobacter pylori infection and chronic atrophic gastritis), bacterial overgrowth and enteric infections, and malabsorption of fat, minerals, and vitamins. A review of the potential gastrointestinal effects of long-term acid suppression with PPI showed that these agents rarely, if ever, produce adverse events.[73] The absorption of fats and minerals does not appear to be significantly impaired with chronic acid suppression. Another prospective study evaluated the safety data of 230 patients with refractory reflux esophagitis treated with omeprazole ≥20 mg daily for the mean period of 6.5 years (range from 1.4 to 11.2 years) found omeprazole was highly effective and safe, without incidence of neoplasm or dysplasia observed.[74] Recent studies reported increased risks of osteoporosis-related fractures in patients taking PPIs for ≥7 years[75] and vertebral fractures in postmenopausal women taking omeprazole.[76] However, after a critical review of all available safety data, a 2008 American Gastroenterological Association Institute found insufficient evidence to recommend for or against bone density studies, calcium supplementation, H. pylori screening, or any other routine precaution in patients taking PPIs.[60]

Efficacy

All PPIs are effective in healing of erosive esophagitis and in symptomatic relief in patients with GERD. Nexium is better for EE as compared to other PPIs, but all PPIs are equally effective in symptomatic control in GERD. PPIs have not been shown to decrease the incidence of esophageal adenocarcinoma.[77]

Patient preference

All PPI are well-tolerated and daily administration increases compliance to therapy. Patients occasionally stop therapy due to headache or diarrhea.

Place in therapy

PPIs are now used as standard of treatment in patients with symptoms of reflux disease, with or without endoscopically proven mucosal damage.

Conclusion

PPIs are the most effective agents, superior to H_2RAs and to placebo, in the treatment of erosive esophagitis and in relieving symptoms of reflux disease. PPI is also effective and safe in maintenance therapy for GERD. BID dosing has limited usefulness.

Prospective Pharmacotherapeutic Agents for GERD

New proton pump inhibitor isomers

The currently available PPIs are racemic mixtures of S and R isomers, which are non-superimposable

images of each other and may significantly differ from each other with respect to pharmacokinetic and pharmacodynamic properties and molecular interaction.[78] Isomers of proton pump inhibitors show a superior metabolic and pharmacokinetic profile as compared to their racemates. The therapeutic efficacy is also superior to the parent racemate. This has been clearly demonstrated with the development of esomeprazole- the S-isomer of omeprazole. S-pantoprazole and dexrabeprazole are new isomers that offer therapeutic advantages as compared to racemic pantoprazole and racemic rabeprazole respectively. Dexrabeprazole 10 mg once daily was better than rabeprazole 20 mg once daily in the improvement and healing of endoscopic lesions and relief from symptoms of GERD.[79] A comparative trial evaluated the efficacy of S-pantoprazole (20 mg once daily) versus racemic pantoprazole (40 mg once daily) in 369 patients.[80] S-pantoprazole was more effective than its racemate in term of symptom relief, but equally effective with respect to healing of esophagitis and gastric erosions. Both of the new isomers (S-pantoprazole and dexrabeprazole) are safe with no adverse reaction reported.[79,80]

Dexlansoprazole is an R-enantiomer of lansoprazole recently received FDA approval as a new PPI. It is indicated for healing of all grades of erosive esophagitis and treatment of GERD. Dexlansoprazole MR (Kapidex) is a novel dual release formulation of dexlansoprazole designed to prolong the plasma concentration-time profile of dexlansoprazole and extend duration of acid suppression with once-daily dosing.[81] Two clinical studies compared lansoprazole 30 mg QD and Kapidex 60 mg QD in treatment of endoscopically confirmed EE. One study showed some superiority at weeks 4 and 8; however, the finding was not replicated in the other (Kapidex product package insert, Takeda Pharmaceuticals America, Inc., January 2009).

New proton pump inhibitors

Tenaprazole (Tu-199) is a novel chemical compound which also belongs to the proton pump inhibitor class. Unlike other PPIs, tenaprazole is characterized by an imidazopyrine backbone, which is responsible for its substantially prolonged half-life (7 hours).[56] In several 24 hour gastric pH monitoring studies, tenaprazole 40 mg was compared to esomeprazole 40 mg and showed to achieve significantly better control of nocturnal acidity than esomeprazole; both had similar control of daytime gastric acidity.[82,83] Further clinical studies are necessary to confirm whether the pharmacological advantages of tenaprazole will be able to be translated into clinical benefits.

Potassium competitive acid blockers

Potassium-competitive acid blockers (P-CABs) represent a new class of drugs acting through a reversible binding mechanism different from the PPIs. In pharmacological studies, they have shown a fast onset of action (within 30 minutes of drug administration) with a maximum effect obtained after the first dose, whereas classical PPIs needs several days to reach their steady-state effect.[56,84] Moreover, P-CABs are active in the absence of stimulated acid secretion and their effect is rapidly reversible. However, these agents are still in early experimental and developmental phases.

Endoscopic Therapies for GERD

GERD is a chronic condition with a high tendency toward relapse when medical treatment is discontinued. Treatment options included long-term use of acid suppression medications or surgical intervention with fundoplication. However, currently available medical therapy does not restore LES function, and long-term drug intake raises issues of compliance, side effects and cost.[85] Surgical therapy in experienced centers offers excellent results, but carries a complication rate of 5% and a mortality rate of 0.2%.[86] Recently, endoluminal therapies have arisen as an alternative to conventional anti-reflux therapy—both medical and surgical. These therapies have been offered to patients who are averse to the long-term complications of prolonged acid suppression therapy, who are responders to medical treatment and are seeking an alternative to surgery.[87]

There are three broad categories for endoscopic therapy to enhance the barrier against acid reflux: (1) radiofrequency treatment to the LES area, (2) techniques using endoscopic sewing/plication devices, and (3) techniques using an injection or implantation of biopolymers into the gastroesophageal junction. Radiofrequency application (Stretta, Curon Medical, Freemont, CA) was designed to increase the reflux barrier of the LES by delivering radiofrequency energy via a flexible catheter and an inflatable balloon to the muscularis layers of the distal esophagus and gastric cardia. This thermal

energy is purposed to alter LES tone by inducing collagen deposition. An initial US open-label study with 6- and 12-month follow-up showed improvement in symptom score related to heartburn, with 34% of patients were back on PPIs and an additional 38% were regularly taking antacid at 1 year.[88] A sham treatment controlled trial was also completed which showed improvement in heartburn quality of life, median heartburn score, and SF 36 physical quality of life in the active treatment group compared to sham therapy.[89] However, there were no differences noted in acid exposure or in the percentage of patient who were able to discontinue daily medications. Reported complications have included death, perforation and hemorrhage. Stretta procedure still currently has FDA approval, but Curon Medical has ceased manufacturing the equipments for the procedure.

Endoscopic anti-reflux treatment using sewing techniques (EndoCinch, Bard, Murray Hill, NJ) was first reported in a study involved 64 participants with 62% of patients in the initial report were off PPIs 6 months after treatment.[90] In a sham-controlled study by Rothstein et al, there were significant differences in heartburn frequency, acid exposure time, and reduction of anti-reflux medication at 3 months.[91] However, extended follow-up of a small number of these patients suggested of only less than 25% of patients were able to remain off medications for 2 years. Recently, a full-thickness plication device (Plicator^{TM}; NDO surgical, Mansfield, MA) has been developed and data from the initial trial showed 74% of 64 studied patients able to be off PPI therapy at 6 months.[92] No serious adverse effects have been reported. A randomized sham-controlled trial showed that improvement in GERD- health-related quality-of-life (GERD-HRQL) score was significantly greater in the active group (56%) compared with the sham group (18.5%, $P < 0.001$) at three months.[93] Complete cessation of PPI therapy and percent reduction in median percent time pH < 4 were also greater in active group compared to those in the sham group. A prospective multicenter trial also showed 66% of the subjects showing 50% or more improvement in GERD-HRQL score and 58% of the patients were off daily PPI therapy at 12 months.[94] A five-year post-treatment follow-up study showed that 67% of patients remained off daily PPI therapy and there was a significant improvement of the GERD-HRQL.[95] There were no long-term procedural adverse side effects observed; all device-related adverse events occurred acutely. Currently, the Davol/Bard EndoCinch and the NDO Plicator are available for commercial use. The EndoGastric Solutions Endoluminal Fundoplication System is also available. Several other suturing/plicating devices have been designed and are undergoing evaluation for endoscopic treatment of GERD. These include the Syntheon Antireflux Device, the Medigus endoscopy system, the Hiz-Wiz device, and several new sewing devices such as the Olympus Eagle Claw.

Various injectable agents have been tested for bulking the gastroesophageal junction to enhance LES pressure as barrier to gastric reflux. Four implantable products have been tested in human: polymethylmethacrylate microspheres (Plexiglas), polytetrafluoroethylene (Polytef), a hydrogel expandable prosthesis (Gatekeeper), and an ethylene vinyl alcoholcopolymer with tantalum dissolved in dimethyl sulfoxide (Enteryx); however, only the last two compounds became available with regulatory approval in the US and Europe. Injection of Enteryx (Boston Scientific, Natick, MA) has been reported to control GERD symptoms and allow 74% of patients to discontinue PPI therapy at 6 months and 70% to discontinue at 12-month follow-up.[96,97] Enteryx was later on withdrawn from the market by the manufacturer in 2005 for severe complications. Endoscopic implantation of the Gatekeeper prostheses (Medtronic, Minneapolis, MN) was studied in a multicenter trial, which showed significant improvement of the primary endpoints, GERD-HRQL and SF-36 score.[98] The most common symptoms reported in the immediate post-procedure period were mild sore throat and retrosternal or epigastric pain. Two patients from this study required hospitalization post-operatively: one patient for intractable nausea that was resolved after the removal of the prosthesis and another patient with pharyngeal perforation. In another small follow-up study, the acid exposure time (AET) was not statistically significantly improved but the GERD-HRQL score was significantly improved at 6 months.[99] The development of Gatekeeper was also suspended in 2005 for lack of long-term efficacy.

All of the endoscopic techniques seem to produce an improvement in reflux symptoms, although significant changes in LES pressure have not been documented and less than 35% of patients

have been demonstrated to have normalization of their intra-esophageal acid exposure by ambulatory pH testing.[3] Unresolved issues remain with the endoluminal therapies, including long-term durability, safety and efficacy. Further investigations are needed.

Concluding Remarks

Gastroesophageal reflux disease is a very common condition that affects approximately 25% of the Western populations and 5% of those have daily symptoms. GERD is a chronic condition that is associated with a range of complications including erosive esophagitis, strictures, Barrett's esophagus, and esophageal adenocarcinoma. Patients with GERD often require maintenance acid suppression therapy to prevent relapse of symptoms and reduce risk of the long-term complications. Available pharmacotherapeutic options for GERD range from OTC antacids and alginates, H_2RAs, mucosal protective agents, prokinetics and drugs that enhance LES pressure to proton pump inhibitors. Only H2RAs and PPIs have shown to be safe and effective, and are the standard of care, in the acute treatment of erosive esophagitis and in long-term maintenance therapy. Prokinetic agents can be useful in selected patients with GERD symptoms while on maximal dosing of PPI therapy; however, the significant side effects profile limits their usefulness in the management of GERD. Various endoluminal therapeutic techniques had been developed as alternatives to surgical fundoplication in patients with partial response to, or who are averse to long-term complications of, chronic acid suppression therapy. Further investigations are needed to assess the safety and long-term benefits of these endoscopic therapies.

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Disclosure

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