GI café

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Current Pharmacotherapies of GERD

According to Montreal consensus “GERD is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications”, where “troublesome” symptoms refers to the symptoms that adversely affect an individual's well-being. The Montreal definition removed the use of term “Nonerosive reflux disease” and grouped GERD into “Esophageal” and “Extraesophageal” GERD syndromes. Esophageal GERD syndromes includes those that are symptom based and those that are defined by the tissue injury. Extraesophageal syndromes are classified by established or proposed association with GERD.

Acid suppression remain the primary approach for GERD management and PPI remains the most potent drug for the management. Approximately one third of the patients with GERD does not respond symptomatically to a standard dose of PPI. Other treatment options such as H2RA, TLESR reducers, prokinetics and alginate has been considered as an adjunctive to standard PPI therapy for symptom relief in patients with PPI, particularly in Refractory GERD. Newer drug as well as different therapeutic approaches targeting the pathophysiology of GERD, other than acid suppression, have also been approached for the patient not responding properly to PPI. In this article a summary of the current and developing options for GERD therapy has been presented.

Antacids and Alginates

Antacids are usually aluminum or magnesium-containing formulations which are weak bases that neutralizes the acidity of the gastric and esophageal contents, providing rapid short term relief from GERD symptoms. In the presence of gastric acid, alginates precipitate, forming a gel, often within a few seconds of dosing. 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. Alginate-containing antacids are comparable to traditional antacids for speed of onset of relief.

Antacids and alginates are a convenient over-the-counter treatment for GERD, but have no efficacy in the healing of erosive esophagitis and only 25% patient experiences symptom relief after their use. They are effective in control of mild to moderate symptoms of reflux disease and promoting healing of duodenal ulcers. They can also be used as an adjunct to PPI therapy for breakthrough symptoms of pyrosis. They are also useful in special populations, where acid suppressive medications may not be the best option.

Mucosal Protective agents

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. Sucralfate is well-tolerated and can be used to promote mucosal healing in cases of gastric or duodenal ulcers. It improves reflux symptoms in patients with reflux esophagitis and non-esophageal reflux disease (NERD) patients. For its low maternal adverse events and no teratogenicity, sucralfate is a safe drug for pregnant woman with reflux symptoms. Misoprostol is routinely used prophylactically in patients who are taking NSAIDs and at high risk of NSAID-induced ulcers, such as the elderly or patients with ulcer complications.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.

Therapy focused on Acid Suppression

Histamine H_2 Receptor Antagonists:

H2RA acts by reducing gastric acid output and the volume of gastric acid by competitive inhibition of Histamine at H_2 receptors and decreased pepsin secretion. H2RA's were the first acid suppressive agent that showed better efficacy in healing erosive esophagitis and relieving reflux symptoms in comparison to Antacids and alginates. H2RA therapy for acute or episodic reflux symptoms are safe and effective and were also used in gastric and duodenal ulcers, acute stress ulcers, and for Zollinger-Ellison syndrome. Although they are effective in promoting healing of gastric and duodenal ulcers, they are less effective in treating esophagitis.

Proton Pump Inhibitors (PPI)

Proton pump inhibitors (PPI) are most effective for the management of GERD. At standard dose PPI's suppresses more than 90% of the basal and gastric acid secretion. The suppression begins within one to two hours of administering the first dose. All PPI's are effective in healing of erosive esophagitis and in symptomatic relief in GERD. Long term use of PPI had areas of concern like carcinoid formation, development of gastric adenocarcinoma, bacterial overgrowth, enteric infections, and malabsorption of fat, minerals and vitamins. But these claims were not found to be statistically significant in further reviews. In 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”. PPIs are superior to H2RAs and are treated as standard of treatment in patients with symptoms of reflux disease, with or without endoscopically proven mucosal damage.

Newer proton Pump Inhibitors

Traditional PPIs (omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole) have relatively slow onset of action and provide insufficient 24-hour suppression of gastric acid under a once-daily dosage regime. Novel PPIs have been designed to improve the PPI efficacy with the advantage of rapid onset of action, extended-released profile, and longer half-life.

Tenatoprazole is a newer, novel PPI has longer plasma half-life in comparison with other PPIs, providing a prolonged duration of acid inhibition and a shorter nocturnal acid breakthrough. Even though the plasma half-life is about seven times longer than that of other PPIs, tenatoprazole is considered a good alternative PPI for patients with ineffective once-daily PPI therapy.

Unlike DR PPI, immediate-release (IR) omeprazole is a formulation of nonenteric-coated omeprazole combined with sodium bi carbonate, which protects omeprazole from degradation by gastric acid, and is characterized by more rapid onset of antisecretory action compared with conventional PPIs. Based on administration time, IR omeprazole provides profound control of postprandial and nocturnal intragastric acidity. IR omeprazole also provided better nocturnal gastric acid control than lansoprazole and comparable efficacy with esomeprazole, suggesting that immediate-release omeprazole may be useful in treating night time heart-burn.

Extended-release(ER) rabeprazole is designed to provide initial acid suppression similar to conventional PPI and maintain the plasma exposure of PPI over a longer period, achieving sufficient duration of acid suppression over a 24-hour period. Once-daily ER rabeprazole demonstrated a significantly longer gastric acid suppression (mean percentage of time with gastric pH>4) over a 24-hour period compared with esomeprazole 40mg and standard DR rabeprazole 20mg.

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.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.

Conclusions

Pharmacotherapeutic options for GERD range from OTC antacids and alginates, H2RAs, 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.

Ref : Wang Y-K, Hsu W-H, Wang SS, Lu C-Y, Kuo F-C. Current Pharmacological Management of Gastroesophageal Reflux Disease

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The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage

Non-Steroidal anti-inflammatory drugs (NSAIDs) are widely used to provide effective pain relief in musculoskeletal problem, chronic arthritis and in inflammatory conditions. Around 30 million people worldwide take NSAIDs on a daily basis, and about 40% of them are older than 60 years. The benefits of NSAIDs, especially in traditional NSAIDs comes at a risk of gastrointestinal adverse effects, ranging from dyspepsia and peptic ulcer disease (PUD) to more serious and potentially life threatening complication such as haemorrhage or perforation. Although adverse effects only occur in a small proportion of individuals, widespread use of NSAIDs has resulted in a substantial number of individuals experiencing serious gastrointestinal (GI) complications. It is estimated that 10-20% of NSAID users report dyspeptic symptoms, and 5-15%of rheumatoid arthritis (RA) patients taking NSAIDs are expected to discontinue medication because of dyspepsia. While endoscopic ulcers can be documented in up to 40% of chronic NSAID users, it is estimated that as many as 85% of these never become clinically apparent. Serious NSAID induced GI complications such as haemorrhage, perforation or deaths are much less common, occurring collectively with an incidence of about 1.5% per year. Use of NSAIDs has also been associated with damage to the small intestine and the colon that may result in complications such as small bowel perforation, bleeding and strictures. However, the number of individuals prescribed NSAIDs and the potential for life-threatening adverse events make NSAID toxicity an important clinical problem.

Two major issues confront clinicians using these agents: 1) the prevention of NSAID-induced ulcers, especially in high risk groups as well as the mucosal damage in small bowel and colon, and 2) their treatment, often when underlying disease mandates continued NSAID use. The GI damage caused by NSAIDs can be ameliorated in a number of ways - most effectively by stopping the drug, by selecting a less toxic NSAID or by adding a second drug, either prophylactically or following a complication. This article focuses on role of Proton Pump Inhibitors (PPIs) in treating and preventing mucosal damages related to NSAIDs.

Risk factors for NSAID induced gastroduodenal damage

Gastroduodenal damage does not occur in all patients taking NSAIDs and is not readily predicted by symptoms. Factors that have been reported to place patients at higher risk of NSAID-related gastrointestinal complications include prior history of gastroduodenal ulcer or haemorrhage, aged 65 years or older, prolonged use of high dose NSAIDs, use of more than one NSAID, concomitant use of corticosteroids or anticoagulants and chronic debilitating disorders, such as cardiovascular disease, renal or hepatic impairment, diabetes or hypertension.

Treatment of NSAID-associated ulcers

Treatment guidelines for NSAID-induced ulcers recommend discontinuation of the NSAID and treatment with any approved therapy for peptic ulcer disease. NSAID-associated ulcers heal at the same rate as non-NSAID-induced ulcers, when NSAID is discontinued. H2RAs heal almost all NSAID ulcers when the patient stops NSAID use. The rate of ulcer healing with H2RA therapy decreases significantly, however, if the patient cannot discontinue NSAIDs.

PPIs are the treatment of choice for NSAID induced ulcers not only after NSAID discontinuation but also in cases where it is not possible to discontinue the NSAID. Use of a PPI has been shown to be associated with ulcer healing and prevention of relapse in patients requiring long term NSAID therapy. Two large multicentre studies of the healing of NSAID induced ulcers have compared omeprazole with misoprostol and ranitidine. The overall rates of successful treatment of ulcers, erosions and symptoms associated with NSAIDs were similar for omeprazole (20 or 40 mg/day) and misoprostol (800mg/day). Omeprazole (20 or 40 mg/day) was more effective than ranitidine (300mg/day) for healing ulcers in patients who took NSAIDs regularly.

Pantoprazole is highly effective in healing ulcers associated with ongoing NSAID therapy. In a comparative study, 120 *H. pylori*-negative patients who had NSAID-associated ulcers, but who were continuing with NSAID therapy, were randomized to receive pantoprazole 40 mg/day, omeprazole 20 mg/day or misoprostol 800mg/day. Pantoprazole appeared to heal ulcers more rapidly than omeprazole or misoprostol, although all the ulcers had healed after 8 weeks of therapy.

Proton pump inhibitors for the prophylaxis of NSAID-related ulcers

Patients with healed NSAID-induced ulcers are among those at highest risk of further gastroduodenal injury, leading to serious complications such as perforation and bleeding. Gastroprotective therapy is recommended for this group of patients if they continue to take NSAIDs. PPIs are particularly suitable in this population, because they have been shown to be equivalent to and better tolerated than misoprostol and superior to ranitidine and placebo in the prevention of recurrence of healed ulcers in patients on long-term NSAID therapy.

A number of clinical studies have been designed to investigate the efficacy of PPIs in the prevention of NSAID-induced gastrointestinal damage. Six randomized controlled trials (RCTs) with 1,259 participants assessed the effect of PPIs on the prevention of NSAID-induced upper GI injury. PPIs significantly reduced the risk of both endoscopic duodenal ulcers [RR = 0.20; 95% confidence interval (CI) = 0.10 to 0.39] and gastric ulcers [RR = 0.39; 95% CI = 0.31 to 0.50] compared with placebo. The results were similar for both primary and secondary prophylaxis trials.

Cycylooxygenase-2 (COX2) NSAIDs versus conventional NSAIDs plus proton pump inhibitors

The two prevailing approaches to decrease risks of nonsteroidal anti-inflammatory drug (NSAID)-associated gastrointestinal (GI) events are the use of a COX-2 inhibitor or co-therapy with a proton-pump inhibitor (PPI). A major limitation of each approach is that, in patients at the highest risk for NSAID-induced ulcers, neither treatment is effective when used as a stand-alone strategy. Two RCTs have addressed this question and support the similarity of each of these risk-reducing approaches. The studies failed to show a safety advantage for using a COX-2 inhibitor instead of a traditional NSAID in high GI risk patients who take PPIs. Thus, there continues to be no prospective data to support a GI benefit of COX-2 inhibitor plus a PPI over traditional NSAID plus a PPI in high-risk patients. A recent case-control study from Canada has provided compelling real-world evidence. Targownik and colleagues observed that any of the gastroprotective strategies - nonselective NSAID + PPI, nonselective NSAID + misoprostol, COX-2 selective NSAID alone and COX-2 selective NSAID + PPI - were all associated with a significantly reduced risk of developing an upper GI complication.

Summary of recommendations for prevention of NSAID-related ulcer complications

	Gstrointestinal risk*		
	Low	**Moderate**	**High**
Low CV risk	NSAID alone (the least ulcerogenic NSAID at the lowest effective dose)	NSAID + PPI/minsoprostol	Alternative therapy if possible or COX-2 inhibitor+PPI/misoprostol
High CV risk* (low-dose aspirin required)	Naproxen + PPI/misoprostol	Naproxen + PPI/misoprostol	Avoid NSAIDs ro COX-2 inhibitors. Use alternative therapy

Gastrointestinal risk is stratified into low (no risk factors), moderate (presence of or two risk factors) and high (multiple risk factors or previous ulcer complications or concomitant use of corticosteroids or anticoagulants). High CV risk is arbitrarily defined as the requirement for low-dose aspirin for prevention of serious CV events. All patients with a history of ulcers who require NSAIDs should be tested for *H. pylori* and if the infection is present, eradication therapy should be given.

COX-2 selective agents were no more likely to reduce risk than PPI cotherapy and the combination of a COX-2 selective NSAID with a PPI was associated with the greatest risk reduction. In summary, the risks of further ulcer complications with conventional NSAIDs plus PPI co-therapy and COX-2 NSAIDs are comparable for high-risk patients. The combination of COX-2 NSAID and PPI co-therapy can further reduce this risk.

***H. Pylori* eradication**

There is a potential advantage of testing for *H. pylori* infection and eradicating the infection if positive in patients requiring long-term NSAID therapy. A comprehensive meta-analysis of 16 case - controlled studies demonstrated that the risk of peptic ulcer bleeding was increased by a factor of 1.79 with *H. pylori* infection, by 4.85 with NSAID usage and by 6.13 in the presence of both NSAID use and *H. pylori* infection, strongly suggesting an additive effect.

The eradication of *H. pylori* in high risk patients prior to the initiation of NSAID therapy has been shown to significantly reduces the risk of subsequent ulceration. Two systematic reviews have consistently shown that eradication of *H. pylori* is superior to placebo in the primary prevention of peptic ulcers among NSAID users [risk ratio (95 % CI) 0.35 (0.20 - 0.61)]. Using a Markov model, a sensitivity analysis showed that the most cost-effective strategy for primary prevention of NSAID-associated ulcer was *H. pylori* eradication in patients above the age of 50 years and the eradication therapy remained cost-effective to *H. pylori* prevalence as low as 5%. Whether co-therapy with a gastroprotective agent is needed after eradication of *H. pylori* depends on individual patients underlying gastrointestinal risk.

Conclusions

Gastrointestinal toxicity related to NSAID drug administration is a growing problem. Because NSAIDs are predominantly used in elderly people and as this cohort of the population is steadily growing over time, physicians are likely to encounter more people using NSAIDs who are consequently at risk of ulcer and its complications. Large clinical trials have consistently demonstrated that PPIs are more effective and better tolerated than H2-receptor antagonists and prostaglandin analogues in the prophylaxis and treatment of drug-related.

Ref : Scheiman JM. The use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage. Arthritis Research & Therapy. 2013 Jul 24;15(Suppl 3):S5.

Proton Pump Inhibitors in the Management of Non Erosive Reflux Disease

Symptoms of gastroesophageal reflux disease (GERD) are very common, affecting up to 20% of the population in America, 9% to 17% of Europe, 12% to 15% of Australia, and 2% to 5% of Asia once a week. Nonerosive reflux disease (NERD) is the most common presentation of GERD. Traditionally, it has been assumed that patients with GERD symptoms who lack esophageal mucosal injury represent a mild form the disease and thus has been treated conservatively with lifestyle modifications, over the-counter H2RA or standard-dose H2-blockers. It is worth mentioning that symptoms and esophageal lesions do not necessarily exist together. A proportion of patients with erosive esophagitis have no symptoms, whereas 50-85% of patients with typical reflux symptoms have no endoscopic evidence of erosive esophagitis.

There are some important developments that have emerged in the field of GERD with emphasizing the importance in managing those patients with NERD. It has been observed that most of the community-based GERD patients appear to have NERD. In addition, previous studies have shown that NERD patients appear to be less responsive to proton pump inhibitors (PPIs) as compared with patients with erosive esophagitis. In clinical practice, patients with reflux symptoms and negative endoscopic findings can be classified as (1) acid reflux-related NERD (increased acid reflux), (2) weakly acid reflux-related NERD (weakly acid reflux with positive symptom association; hypersensitive esophagus), (3) non acid reflux-related NERD (nonacid reflux with positive symptom association), and (4) functional heartburn (no associations between symptoms and reflux).

Pathophysiology of NERD

The main physiological cause of reflux oesophagitis remains exposure of the oesophagus to gastric acid. The majority of patients with erosive reflux oesophagitis can be cured by acid suppression, by means of a PPI. Excessive gastric acid exposure remains the main cause of NERD, but NERD may also be associated with Incomplete acid suppression, Oesophageal hypersensitivity to acid, Oesophageal hypersensitivity to distension, Reflux of duodenal juice (bile and pancreatic juice), Oesophageal motility abnormalities, Sustained oesophageal contraction, Psychological factors, and Eosinophilic oesophagitis.

Clinical features

Currently, there are no clinical features that can differentiate NERD from erosive oesophagitis, or even Barrett's oesophagus. There are also no clinical predictors for patients with functional heartburn. This means that these patients cannot be identified on a clinical basis only. Severity, frequency, or intensity of symptoms, have been shown to be similar, consistently, among the different reflux disease phenotypes. Furthermore, patients with different degrees of oesophageal acid exposure have a similar symptom presentation. The two cardinal symptoms of NERD patients are also heartburn and acid regurgitation. A careful physical examination is required on presentation and on subsequent visits, as needed. Most patients with NERD do not demonstrate any specific disease-related physical findings.

Diagnosis of True NERD

NERD should be suspected in every patient who presents with typical, or extra-oesophageal, manifestations of GERD. Currently, there are no clinical predictive factors that can help determine if patients have erosive oesophagitis or Barrett's oesophagus, or if they lack oesophageal mucosal injury. Regardless, patients presenting with symptoms of heartburn and acid regurgitation (unless symptoms that cause alarm are present), are likely to be, and should be, treated empirically with an anti-reflux medication.

Endoscopic Image: Currently, NERD is differentiated from erosive esophagitis by white light endoscopy, and NERD is further differentiated from functional heartburn by using pH monitoring (±impedance) with symptom reflux association. Recent technological advances may improve diagnostic sensitivity regarding upper endoscopy. Due to a significant overlap in the amount of reflux episodes between patients with NERD and erosive esophagitis, it is suggested that mucosal changes in NERD patients may be too subtle to be detected by conventional endoscopy. A concern has been raised about over diagnosing NERD during endoscopy, because of the common use of anti-reflux medications, and because patients are already on such medications.

24-Hour Impedance pH Monitoring: 24-hour esophageal pH monitoring has been criticized for having limited sensitivity in diagnosing GERD; however, this technique is still highly valued for the diagnosis of NERD. The limitation of conventional pH monitoring has been overcome by combining pH with impedance monitoring. 24-hour impedance pH monitoring enables detection of acidic, weakly acidic and non-acidic reflux and correlation with symptoms. This technique is able to identify three subsets of NERD (i.e., patients with an excess of acid, with a hypersensitive esophagus [to weakly acidic reflux] or with nonacid-reflux related symptom) and patients with functional heartburn. Performing 24-hour oesophageal pH monitoring for the purpose of subcategorising NERD patients is not practical in clinical practice.

Treatment of NERD

The majority of patients with symptomatic reflux are managed by their family physician. Referral to a specialist is usually reserved for those with any symptoms that cause alarm, or those who do not obtain an adequate response to the trial of therapy. The goals of treatment is Acute and long-term relief of symptoms, Maintenance of clinical remission, and Restoration of quality of life.

PPIs are the most recommended and effective agents employed in the treatment of GERD. The advantage of PPIs relieving reflux symptoms is also found in NERD patients. PPIs are more effective than other acid-suppressing agents such as histamine-2 receptor antagonists (H2RAs). Initially, patients can be treated by a proton once daily standard dose PPI for 2-4 weeks. If initial treatment fails to elicit adequate symptom control, increasing the PPI dose (standard dose PPI twice daily) is recommended.

Studies have demonstrated that on-demand or intermittent PPI therapy is an effective strategy in NERD treatment. Due to the fact that most of the NERD is less likely to be progressive, treatment for those patients can be tailored by the presence of their symptoms. Therefore, on-demand or intermittent therapy is widely used as alternative PPI treatment for NERD patients, which also has the advantage of convenience, stable acid control, cost effectiveness, and reducing the chance of acid rebound.

Complications

Thus far, clinical evidence is lacking to indicate that patients with NERD are at risk of developing any of the typical complications of GERD over time, i.e. Barrett's oesophagus or adenocarcinoma of the oesophagus. The main impact of the disease is on patient's perceptions of their quality of life.

Conclusion

NERD is the most common presentation of GERD in community based patients with moderate-to-severe symptoms, and causes a significant impairment in quality of life. Therapy with PPIs results in improvement or complete resolution of symptoms in most NERD patients, and restores quality of life. The majority of patients with reflux symptoms are effectively managed by empiric PPI therapy prescribed by their family physician, without knowing whether they have erosive or non erosive disease.

Ref: Chen C-L, Hsu P-I. Current Advances in the Diagnosis and Treatment of Non-erosive Reflux Disease

Congratulations!

The Winners of GI café Quiz Competition

(July 2013 Volume : 6 Issue : 1)

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Editorial Note:

Dear Doctor, It's our immense pleasure to inform you that we have published the 2nd issue, 2013 of GI Café. In this issue we try to focus on Current Pharmacotherapies of GERD, the use of proton pump inhibitors in treating and preventing NSAID-induced mucosal damage and Proton Pump Inhibitors in the Management of Non Erosive Reflux Disease. Your comments and suggestions will enrich our upcoming issues. Please participate in quiz competition and win prizes.