Treatment of Peptic Ulcer; Current Status And Potential Strategies

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Abstract: Peptic ulcer is disease of the gastric mucosa in which there is erosion and inflammation. The disease is caused by the imbalance between the bicarbonate and acid that is generated in the gastric and duodenal area of the gastrointestinal tract. Ulcers can develop in the esophagus, stomach or duodenum, or at the margin of a gastroenterostomy, in the jejunum, in Zollinger-Ellison syndrome, and in association with a Meckel's diverticulum containing ectopic gastric mucosa. Peptic ulcer disease is one of several disorders of the upper gastrointestinal tract that is caused, at least partially, by gastric acid. Gastric acid secretion is regulated by an extensive collection of neural stimuli and endocrine and paracrine agents, which act either directly at membrane receptors of the parietal cell or indirectly through other regulatory cells of the gastric mucosa, as well as mechanical and chemical stimuli. In this review, we have tried to condense the current body of knowledge about the modulating action of inflammatory mediators on the pathophysiology of gastric acid secretion and update its significance based on recent findings in gastric mucosa and parietal cells in humans and animal models as well the current and potential strategies for its therapy.

Keywords: Ulcer, PUFA, mucosa, inflammation, carbonic anhydrase, stem cells

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I. Introduction

Peptic ulcer disease is characterized by inflamed lesions or excavations (ulcers) of the gastric mucosa and underlying tissue of the upper gastrointestinal tract. The ulcers are caused by the damage to the mucous membrane that normally protects the esophagus, stomach and the duodenum from the gastric acid and pepsin. The damage can be caused by several factors, including excessive acid and pepsin production, bile acid reflux, advancing age, ischemia and in many cases infection with Helicobacter pylori bacteria and inhibition of the prostaglandins (1). Oxidative stress has been found to be the major pathogenic factor in the progression of ulcer that directly impairs the cellular functions and promotes cellular organelles damage in the cells, including mitochondria and nucleus. The nitric oxide (NO) is accepted as a vital mediator of GIT mucosal defense as decreased NO generation or synthesis contribute to the pathogenesis of ulcer disease (2). Recent findings show significance of polyunsaturated fatty acids (PUFAs) in numerous clinical ailments, so observing the consequence of PUFAs in several of the clinical situations. On the other hand it was suggested that insufficiency of PUFAs in particular the gamma-linoleic acid, di-homo-gamma-linolenic acid and eicosapentanoic acid might be accountable for the development of peptic ulcers (3,4). PUFAs hold the capacity to obstruct the development of H.pylori, decrease the acid formation and release in experimental animals, in individuals and also in the improvement in the condition by amplifying the action of PGE1 prostaglandin. There has been substantial progress in the understanding of the peptic ulcer patho-physiology and its treatment. This review tries to encompass some of the recent developments relating to this chronic disorder.

1. Helicobacter Pylori and recent advances in its pathological role in ulcers

In the Western countries, the number of persons who harbour the H.pylori increases from under 5 % at birth to about 20 % and at the age of 45 years only a small proportion of persons harbouring this bacterial organisms will develop this disease. H.pylori induced gastritis precedes the development of peptic ulcers in most cases. H.pylori is found at gastrointestinal tract of duodenal ulcers and 70% patients of gastric ulcers (5). The organism is known to attach to the mucosa and mucosal epithelial cells and release enzymes that damage the mucous membrane and mucosal cells and cause inflammation and tissue destruction. Evidence also suggests that eradication of H.pylori heals peptic ulcers and reduces recurrence of duodenal and gastric ulcers. Approximately 10% of those infected with the H.pylori will develop peptic ulcer disease. The bacterial genetic locus most closely associated with the development of peptic ulcer and gastric cancer is the H.pylori Cag pathogenicity island (Cag PAI) a 40 kb DNA segment that
encodes a type IV secretion that encodes a type IV secretion system (6).

1.2 Influence of Adenosine in gastric acid secretion

The exact role adenosine has in the parietal cell function or the gastric gland physiology in humans is not well delineated. Although findings in the human gastric mucosa are the most attractive and important for obvious reasons, the inference is inconclusive yet. Studies addressed adenosine deaminase (ADA) activity in mucosal biopsies in patients with a diversity of pathologies. Adenosine considered to have an anti-inflammatory action (7). However, in H. pylori-infected patients or in patients with chronic gastritis (8), no correlation between ADA activity and mucosal inflammation was found. A positive correlation between ADA activity and basal and maximal gastric acid output was found in the fundic mucosa, suggesting a protective, negative influence of adenosine on acid secretion from fundic parietal cells. However, considering the low proportion of H⁺/K⁺-ATPase positive cells in the fundic area of the human stomach and that 95% of parietal cells were found within the oxyntic mucosa of the stomach (9), the physiologic relevance of these findings may be under scrutiny. Given the differences between species, extrapolation of the findings in animal models to humans should be avoided (Fig. 1).

![Fig. 1: Innervation of the gastric mucosa (Courtesy: Rosa M Amin et al, Front. Physiol. 8:737, 2017)](image_url)

1.3 Role of Ghrelin and somatostatin

Ghrelin is a peptide that defines the anatomical body of the human stomach and seems to induce acid secretion and hunger by stimulating histamine production by ECL cells (10). Other compounds have been also reported to affect directly or indirectly gastric acid secretion. The effect of compounds like interleukin-1β, neurotensin, nitric oxide, oxyntomodulin, secretin, and serotonin is most likely inhibitory, although it remains a matter of debate (11). Somatostatin is the main negative regulator of acid secretion. It is a hormone and paracrine peptide produced in the stomach by D cells. These cells are present in the oxyntic mucosa, where they negatively regulate ECL and parietal cell function, and also in the antral mucosa, where they negatively regulate G cell function (12). The physiology and morphology of both cell populations is also different. D cells secrete somatostatin in response to several stimuli. One of them is gastrin, which induces somatostatin secretion, which in turn inhibits gastrin secretion from G cells. Therefore, the gastrin-somatostatin axis constitutes a negative feedback mechanism that maintains gastrin levels and acid secretion under control. Another positive stimulus is cholecystokinin (CCK), a peptide hormone secreted by the small intestine I cells as a response to luminal lipids; by stimulating somatostatin secretion CCK inhibits acid secretion during intestinal digestion. Luminal pH is probably the most important inducer of somatostatin release. Antral D cells are often called open type, because they possess extensions that make contact with the luminal content (13).

1.4 Nanolipobead based drug delivery system for treating peptic ulcer

Artificial particulate systems such as the polymeric beads and liposomes are finding a variety of biomedical applications in drug delivery, drug targeting, protein separation, enzyme immobilization and in
blood cell substitution. Liposomes have a flexible, cell-like lipidbilayer surface which acts as a permeability barrier such that compounds can be entrapped in their aqueous interior. However, liposomes can be mechanically unstable and their loading capacity limited by the water solubility of the material to be loaded. Polymeric beads, although mechanically more stable and having a larger loading capacity then liposomes, lack many of the useful surface properties of a lipid bilayer shell (14-15). Recently the preparation and characterization a new hybrid vesicle system with structural similarity to natural cells that combines complementary advantages of liposomes and polymeric beads this system which have been called ‘Lipobeads’ consists of a lipid bilayer shell that is anchored on the surface of a hydrogel polymer core. 

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1.5 Gastroprotective role of PUFA

Amongst the long chain PUFAsthe Omega-3 (n-3) polyunsaturated fatty acids [n-3 PUFA, eicosapentaenoic acid (EPA 20:5n-3), and docosahexaenoic acid (DHA 22:6n-3)] are the PUFAsthe eicosanoids which are essential fatty acids as they are synthesized by mammals from other dietary precursors which contain n-3 PUFAsthe. They are sufficiently found in fish. Fatty acids are key nutrients affect early growth and development and preventing chronic disease in later life (18). PUFAsthe that contain more than one carbon double bond are divided into two major classes, namely, the n-6 and n-3 (Figure 1). Several lipid metabolites can be made from these PUFAsthe. Linoleic acid (LA 18:2n-6) is a representative n-6 PUFAsthe, which is the precursor of arachidonic acid (AA 20:4n-6) which is involved in inflammation, inducing cardiovascular diseases, diabetes, cancer, and age-related diseases. n-3 PUFAsthe suppressed the activation of EGFR, PKC and interleukin-6 levels.

Sardine oil contains comparatively high amount of PUFAsthe and n-3 PUFAsthe dominant among fatty acids (19). The gas chromatographic analysis of Sardine (Sardinella longiceps) fish oil highlighting nutritionally significant n-3 PUFAsthe (like EPA and DHA) and they contribute to the major bioactivity of the oil. The protective effects were linked to their anti-oxidant properties. The the anti-inflammatory activity of these n3 and n6 containing PUFAsthe containing oils reduced the TNF alpha levels and increased the PGE2 levels. This treatment offers cytoprotection by increasing inhibition of TNF-α and neutrophil infiltration in mucus. Thus these PUFAsthe containing oils ultimately inhibit tissue destruction by reactive oxygen showed good gastro-protective anti-ulcerogenic activity. The data obtained from studies carried out by this author suggests that the PUFAsthe containing oils used in this study i.e. the fish oil and Arasco oil the n-6 PUFAsthe contained in Arasco oil were able to attenuate the ulcer formation as calculated based on the ulcerindex (21). Dietary supplementation with n-6 fatty acid rich in LA has been found to influence the physiological function of various blood components, producing an inhibitory effect on mononuclear cell adhesion, platelet count, platelet aggregation and collagen formation. Dietary supplementation with n-3 PUFAsthe improved colonic anastomoses healing. n-3 PUFAsthe enhance the colonic wound healing in a rat model. Actually, n-3 PUFAsthe may prompt faster resolution of inflammationwithin the wound microenvironment, which leads tofacilitated regeneration and re-epithelialization. A small randomized controlled trial evaluated a formula supplemented with fish oil in patients with pressure ulcers and noted decreased progression of pressure ulcers in those receiving fish oil supplementation. There is growing evidence that the diverse biological roles of n-3 PUFAsthe contribute to their regenerative actions against chronic inflammatory disease.
inhibition (23). Correlating in vivo results with the data obained in vitro suggests that gastric mucosa CA I, II, and IV inhibition is induced by sulfaenamide, the active form of omeprazole, thus this class of compound can be interesting leads for futhere exploration of anti-ulcer action (Table 1).

1.7 Association of peptic ulcer disease with anthropometric, blood parameters and nutrition:

Recent findings are consistent with the results of previous studies; specifically, as it was found that weight, hip circumference (HipC), and BMI in women and HipC in men were highly associated with peptic ulcer disease (PUD) in both the crude and adjusted analyses. Therefore, it was suggested that PUD may be associated with anthropometric indices such as weight, BMI, and HipC in women, but not in men, although there was not a strong association between PUD and anthropometric indices in the Korean population (24-26). Regarding nutritional components, some studies have argued that high dietary fiber intake is associated with PUD, gastric cancer, and gastroesophageal reflux disease, when compared with low dietary fiber intake, and that intake of vitamin A and C is related to PUD. Anderson and colleagues suggested that a high intake of dietary fiber reduced the risk of gastrointestinal and duodenal ulcer, coronary heart disease, diabetes, obesity, and stroke. Additionally, Ryan-Harshman and Aldoori reported that a high-fiber diet and soluble fiber intake appeared to decrease the risk of duodenal ulcer (27). Aldoori and colleagues reported that dietary fiber intake was inversely related to the risk of duodenal ulcer in US men when comparing the highest and lowest quintiles of dietary fiber intake. In another study, Aldoori and colleagues found that vitamins A and E were associated with the risk of duodenal ulcer and that vitamin A and fiber could possibly reduce the development of duodenal ulcer. They argued that vitamin B2 and potassium were inversely associated with the risk of duodenal ulcer. Miyake and colleagues reported that a lack of water-soluble vitamins could accelerate the development of PUD in Japanese adults (28). Additionally, Aditi and Graham documented that Vitamin C (ascorbic acid) plays a very important role in the conservation and treatment of the gastric mucosa and that deficiency in vitamin C has repeatedly been linked with PUD (29).

1.8 Stem cell based therapy for peptic ulcer

Stem cell based transplantation has been found to be effective for the treatment of various disorders. Engevik and colleagues show that gastric stem cells isolated from young mice can be transplanted into sites of injury within the stomach of older mice, and that this results in accelerated repair (30). The ability of the transplanted young mouse cells, but not stem cells from older mice, to differentiate into a specialized cell type, termed SPEM, which is central to the healing process, appears to be a key component of this intervention. While more work needs to be done, it is clear that this approach, or other means of inducing older cells to differentiate into SPEM, would be powerful in treatment of gastric injury. Gastric stem cells isolated from young mice have been experimentally transplanted into older mice with stomach ulcer (31-32). The transplanted cells which replaced cells at the site of injury were observed and found to speed up the healing process. These stem cells from older mice were unable to differentiate into the specialized cell type which is responsible for the healing process.

II. Conclusions

The advent of peptic ulcer disease with time is both complex and interesting. Although its incidences were rare before the 18th century, with time and change in life style its incidences have increased significantly. Various therapeutic strategies have evolved over time for its clinical management. However, considering the involvement of multiple factors in its etiology, it has not been possible to provide an ideal solution to completely cure its manifestations. Traditional use of antacids and use of histamine inhibitors are important for the management of peptic ulcer disease. Irreversible inhibition of proton pump although reduces ulceration, but in the long run leads to adverse issues. It has not been possible to develop an ideal proton pump inhibitor. In this scenario, search for alternatives by capitalizing on the multifactorial etiology of ulceration holds promise. However, these searches are far from over and require further investigations to develop ideal antiulcer agents, although the disease can be substantially controlled by pharmacotherapeutic interventions.

Table 1: Current treatment regimen for H. pylori infected peptic ulcer

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Drugs</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triple therapy</td>
<td>1. Lansoprazole</td>
<td>60 mg/12 hourly</td>
<td>10-15 days</td>
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<tr>
<td></td>
<td>2. Amoxicillin</td>
<td>1g/ 12 hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Clarithromycin</td>
<td>500mg/12 hourly</td>
<td></td>
</tr>
<tr>
<td>Quadruple therapy</td>
<td>1. Lansoprazole</td>
<td>30 mg/12 hourly</td>
<td>10-15 days</td>
</tr>
<tr>
<td></td>
<td>2. Metronidazole</td>
<td>500mg/12 hourly</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Clarithromycin</td>
<td>500mg/12 hourly</td>
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