A REVIEW ON: PEPTIC ULCER

Chaudhary S¹*, Kapila A¹, Sharma RB¹, Vashist H¹, Gupta A¹

¹L.R. Institute of Pharmacy, Solan (H.P.), India

ABSTRACT

A peptic ulcer is a sore on the lining of the stomach or duodenum. The two most common types of peptic ulcer are called gastric ulcers and duodenal ulcers. Peptic ulcers are found to be due to an imbalance between aggressive factors such as hydrochloric acid (HCL), pepsin, refluxed bile, leukotrienes (LTs), reactive oxygen species (ROS) and defensive factors, which include the function of the mucus bicarbonate barrier, prostaglandins (PGs), mucosal blood flow, cell renewal and migration, nonenzymatic and enzymatic antioxidants and some growth factors. H. pylori infection and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) are the predominant causes of peptic ulcer disease. Also a numbers of factors are implicated in the pathogenesis of gastric ulcer, among which major factors involved are bacterial infection (Helicobacter pylori), certain medications (NSAID), chemicals (Hcl/ethanol), gastric cancer and minor factors are stress, smoking, spicy food and nutritional deficiencies. Due to changes in life style and eating habits an increase in frequency to be affected by ulceration in gastric contents can be observed now a day. At the same time a number of semi synthetic and synthetic drugs like proton pump inhibitors, H2 receptor antagonists, and mucosal defensive agents along with various antimicrobial agents are available for the treatment of ulcer.

Keywords: Peptic Ulcer, Types, Pathogenesis and Mediators.

Introduction

Ulcer in the lining of stomach is called gastric ulcers. Peptic ulcer disease is a group of disorders characterized by the presence of ulcers in any portion of gastrointestinal tract (GIT) exposed to acid in sufficient concentration and duration. Although these ulcerations most commonly occur in the stomach (gastric ulcer), or small intestine (duodenal ulcer), this disease also includes Barrett ulcer of the esophagus (Barrett’s esophagus or Barrett’s Metaplasia) and other upper GI ulcers [1]. An ulcer is a crater like lesion in a membrane; ulcers that develop in areas of the GIT exposed to acidic gastric juice are called peptic ulcers [2]. Word ‘peptic’ derives from the Greek term ‘peptikos,’ meaning related to digestion [3]. If there is lining in the duodenum part which is part of intestine below the stomach, they are called duodenal ulcer. The peptic ulcer includes both gastric and duodenal ulcer. It is the term used to describe a break in the lining of any part of the body, but many people will suffer from mouth ulcer affect in their tongue or gums. The stomach wall is protected by the mucosa against irritation of gastric acid. When the mucosa is damaged or when the stomach produces much gastric acid that the protective lining is eroded with subsequent inflammation or necrosis, a local ulcer will develop. The commonest symptom of peptic ulcer is intermittent abdominal pains, especially in the middle of the night or when you are hungry. Other symptoms include bloating, nausea, burping and loss of an appetite. Moreover, NSAIDs along with H. pylori combine the caustic effects of gastric acid and pepsin, which disrupts the normal defense mechanism of the GI mucosa [4]. Various protective and aggressive factors are summarized below [5].

Protective factors
- Bicarbonate,
- Mucus,
- Mucosal blood flow,
- Prostaglandins.

Aggressive factors
- Acid,
- Pepsin,
- Helicobacter pylori,
- NSAIDs.

**Regulation of Gastric acid Secretion**

The terminal enzyme H+K+-ATPase secretes H+ ions in the apical canaliculi of parietal cells, and can be activated by histamine, acetylcholine and gastrin acting via their own receptors located on the basolateral membrane of these cells. Histamine directly acts through H2 receptors followed by generation of cAMP formation, along with Ca2+ mobilization, while acetylcholine and gastrin acts either may act directly through muscarinic and gastrin receptor respectively or may act indirectly by releasing histamine from “histaminocytes”. The muscarinic receptors and gastrin receptors (cholecystokinin receptors) function through IP3-DAG pathway that mobilizes intracellular Ca2+. Gastrin is secreted from the antrum in response of antral pH, food constituents and vagal mediated reflexes. Vagus releases acetylcholine which release histamine and gastrin through the acting on histaminocytes and gastrin secreting cells. Prostaglandins produced by gastric mucosa inhibits acid secretion by opposing cAMP generation and gastrin release. The mechanism of NO is not yet clearly established [6].

**Types of peptic ulcer**

Ulceration of the gastrointestinal mucosa is caused by disruption of normal balance of the corrosive effect of gastric juice and the protective effect of mucus on gastric epithelial cells. On the basis of location, peptic ulcers are categorized as follows:

- Gastric ulcer: means occurrence of ulcer in stomach. These ulcers occur more generally in the older age.
- Duodenal ulcer: Occurrence of ulcer in the duodenum is referred as duodenal ulcer. These ulcers are more common than gastric ulcers. They occur commonly in younger individuals and are evenly distributed among various socio-economic groups. Duodenal ulcer patients have higher than normal levels of acid secretion rates [7-9]. Depending on severity, peptic ulcers are also classified as: Acute peptic ulcers: These ulcers involve tissues to the depth of the sub mucosa. They may arise in the form of single or multiple lesions. They are found in many sites of stomach and in the first few centimeters of duodenum. Chronic peptic ulcers: These ulcers penetrate through the epithelial and muscle layers of stomach wall and may include the adjacent pancreas or liver. In majority of cases, they occur singly in the pyloric antrum of the stomach and in duodenum [10].

**Etiology and pathogenesis of ulcer**

H. Pylori is the main cause of stomach ulcers, was first identified by the two Australian scientists in 1982. H. Pylori is a gram negative bacillus, motile, microaerophilic, flagellated and spiral shaped bacteria [11]. Type I strains of H. Pylori possess a pathogenic activity, that encodes the effectors protein cytoxin-associated gene A (cagA). After translocation into the host cell, cagA effects cell shape, increases cell motility, disturbs cell functional activity and thus responsible for gastric carcinomas and gastric ulcers [12]. H. Pylori causes increases expression of cytokines such as TNF-α in gastritis. Further, IL-1β is too over expressed in the H. Pylori-induced gastritis [13]. H. pylori-infected gastric mucosa showed infiltration of polymorphonuclear leukocytes, lymphocytes, monocytes and plasma cells in the lamina propria, and intraepithelial severe neutrophil infiltration [14]. The appropriate antibiotic regimens can successfully eradicate the infection with complete resolution of mucosal inflammation and a minimal chance for recurrence of ulcers [15]. Triple therapy regimens comprising of a proton pump inhibitor or ranitidine bismuth citrate and two antibiotics (Amoxicillin and Clarithromycin) are the standard therapy to treat H. pylori infection [16].

**Gastric acid secretions**

Gastric acid is established as one of the major ulcerogenic factor for the induction of gastric ulcer disease. It has been reported that about 50% of gastric ulcer patients are pepsin and acid hyper secretors [17]. But, on the other hand, gastric acid plays astringent role in gastric defense. It is the first line of mucosal defense to prevent bacterial colonization and reduced their ability to entrance in the mucosal layer [18]. Acid secretion is suggested to be stimulated by three principle secretagogues histamine, acetylcholine and gastrin. The receptors on the surface of parietal cell include H2 receptors responding to histamine released from specialized mast cells, receptors that are sensitive to the muscarinic effects of acetylcholine released from the vagus nerve and probably receptors responsive to endogenous circulating gastrin [19]. Gastrin stimulates acid secretion either by direct stimulation of parietal cells or by the release of histamine from ECL cells [20,21]. Histamine stimulated acid secretion through a novel histamine receptor, the H2 receptor [22]. Moreover, various studies indicate numerous epithelial cells at the base of pyloric glands contain histamine and histidine decarboxylase (HDC), the enzyme responsible for the synthesis of Histamine [23]. The only source of the acetylcholine (Ach) that can act

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directly on the parietal cell is from the postganglionic fibres of the enteric nervous system. The muscarinic-1 agonist McN-A-343 stimulates acid secretion without affecting histamine release, thus suggesting that the muscarinic receptor on the parietal cell [24].

**NSAIDs (Non-steroidal anti-inflammatory drugs)**

NSAIDs are valuable therapeutics that acts not only as anti-inflammatory, but also as analgesics and antipyretics. They are used in a wide variety of clinical conditions, including arthritis and other musculoskeletal disorders. Unfortunately, their use has been limited by their gastric ulcer-inducing effects. Nearly 25% of chronic users of these drugs develop gastric ulcer disease [25]. Various studies indicates that NSAIDS helps in the progression of ulceration by overcoming the expression of enzyme cyclo-oxygenase (COX) which has been documented to inhibit the conversion of AA to PG’s, that impairs the mucusal barrier and results in corrosive action with pepsin and results in the progression of peptic ulcers [26,27]. Further, COX-1 inhibition by the NSAIDS leads to the significant release of the endothelin-1 (ET-1) which is a potent vasoconstriction which has been shown to induce mucusal injury. NSAIDS by inhibiting the prostaglandin synthesis prostaglandins causes the activation of neutrophil and the local release of reactive oxygen species (ROS) and thus initiates the gastric injury [28].

**Cytokines**

Cytokines play a central role in the regulation of the mucosal immune system, and therefore are extremely important in mucosal defense. Several pro inflammatory cytokines are involved in the pathogenesis of peptic ulcer, like interleukin (IL)-1β, IL-2, IL-6, IL-8 and tumor necrosis factor (TNF)-α. When inflammation of the gastric mucosa occurs, it leads to infiltration of neutrophil and mononuclear cells that stimulates the transcription and leads to the synthesis of several pro inflammatory cytokines [29]. IL-1 has been shown to reduce the severity of gastro duodenal damage and increase the resistance to injury [30,31]. The mechanism underlying the protective actions of IL-1 is not fully understood, but it has been found that IL-1 reduces injury through a paradoxical inhibitory action on leukocyte adherence. Further, IL-1 has also play a role in the inhibition of gastric acid secretion [32-34]. Also, IL-1 stimulates the release of prostaglandin and NO possibly by inducing I-NOS expression and COX-2 expression, thus provide a protection to gastro duodenal mucosa [35]. Furthermore, IL-1 has been shown to inhibit the release of other ulcer:

- Promoting mediators like PAF,
- Histamine from mast cells.

**Prostaglandins**

Prostaglandins are 20-carbon fatty acids produced from arachidonic acid via the enzyme cyclo-oxygenase. Hawkey and Rampton found that prostaglandins exert their cytoprotective actions by stimulating the mucus and bicarbonate secretion, maintaining mucosal blood flow, and by enhancing the resistance of epithelial cells to injury induced by cytoxins [36]. Prostaglandins found to be inhibits the leukocyte recruitment which could contribute to the beneficial effects of these substances in situations in which the GI mucosa is inflamed [37].

**LTs (Leukotrienes)**

Leukotrienes are derived from arachidonic acid through the action of lipoxygenase and are considered to be important mediators of inflammatory and allergic reactions [37]. Two main subclasses of LTs has been suggested, leukotriene B4 and the peptido-leukotrienes (LTC4, LTD4 and LTE4). LTB4 is a very potent chemotaxin for neutrophils, it stimulate the release of reactive oxygen metabolites from neutrophils and contributes significantly to the tissue injury associated with mucosal inflammation. It has been shown that LTs induce vasoconstriction in the vascular bed of the stomach followed by leakage of macromolecules from the post capillary venules [38].

**Treatment of gastric ulceration**

The treatment of gastric ulcer in the horse is actually surprisingly easy. The most effective treatment is a drug called omeprazole, which is marketed as ‘Gastro guard’ and Comes in what looks like a worming tube. It is initially administered at a high dose to treat existing ulcers and then after several weeks the dose is lowered and used as a preventative treatment.

**Conclusion**

Peptic ulcer disease remains a frequent clinical problem in our environment predominantly affecting all age of people. As the prevalence of peptic ulcer disease increases with advancing age it is expected that this common disease will continue to have a significant global impact on health-care delivery, health economics and the quality of life of patients.

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