

## REVIEW ARTICLE

# PATHOGENESIS OF PEPTIC ULCER DISEASE AND CURRENT TRENDS IN THERAPY

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**Abstract** : Traditionally drugs used in peptic ulcer have been directed mainly against a single luminal damaging agent i.e. hydrochloric acid and a plethora of drugs like antacids, anticholinergics, histamine H<sub>2</sub>-antagonists etc. have flooded the market. An increase in 'aggressive' factors like acid and pepsin is found only in a minority of peptic ulcer patients. These factors do not alter during or after spontaneous healing. It is well-known that the gastric mucosa can resist auto-digestion though it is exposed to numerous 'insults' like high concentration of hydrochloric acid, pepsin, reflux of bile, spicy food, microorganisms and at times alcohol and irritant drugs. It is thus evident that the integrity of the gastric mucosa is maintained by defense mechanisms against these 'aggressive' damaging factors. Recently, attention has been focussed more on gastroduodenal defense mechanisms leading to the concept of 'Cytoprotection'. The old dictum "no acid - no ulcer" now extends to "if acid - why ulcer"? as a fundamental question. During last decade more information has poured in about the prevalence and changing pattern of the disease, the influence of environmental factors and speculation on the role of a recently characterized bacterial organism, *Helicobacter pylori* which colonizes in the gastric mucosa, particularly the antral region. This review briefly describes current knowledge about the pathogenesis of peptic ulcer disease and discusses strategies for its treatment.

**Key words** : gastric ulcers                      duodenal ulcers                      *Helicobacter pylori*  
NSAIDs anti-secretory agents

## INTRODUCTION

Gastric and duodenal ulcer or peptic ulcer disease (PUD), Zollinger-Ellison Syndrome (ZE) and gastroesophageal reflux disease (GRD) are upper gastrointestinal disorders sharing a common abnormality : too much acid and pepsin activity for the degree of local tissue resistance. Hydrolytic and proteolytic digestion of the exposed mucosa occur followed by inflammation, necrosis and ulceration. Gastric hypersecretion appears to be the primary causative event at

one end of the disease spectrum as 93% of the patients afflicted with Zollinger Ellison Syndrome is characterized by single or multiple non-beta islet cell adenomas of the pancreas which releases large quantities of gastrin in plasma resulting in a 10-20 fold increase in the amount of acid secreted and a high incidence of ulcers. At the opposite end of the spectrum acid secretion plays a lesser role and mucosal resistance becomes more important. Gastric ulcers are typified by a reduced basal and stimulated acid output. Some acid is however,

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always required as peptic ulcer disease rarely develops in patients of achlorhydria. The other causes of peptic ulcer disease include *Helicobacter pylori* infection, non-steroidal anti-inflammatory agents (NSAIDs) and malignancy. Recent evidence relates *H. pylori* to the pathogenesis of chronic duodenal ulceration as *H. pylori* infection and antral gastritis are found together in more than 95% of patients with duodenal ulcer. *H. pylori* is a very powerful producer of urease and may cause ulceration by causing hydrolysis of urea which leads to generation of cytotoxic ammonia. The NSAIDs when administered orally cause local irritation, allow back diffusion of acid into the gastric mucosa and induce tissue damage, whereas, parenterally administered NSAIDs can also cause gastric mucosal damage and bleeding correlated with the inhibition of the biosynthesis of gastric prostaglandins (PG) especially PGI and PGE.

***Defense of normal gastric mucosa against aggressive factors:***

Three basic levels of defense underlie the remarkable ability of normal gastroduodenal mucosa to resist injury from the acid and peptic activity in gastric juice.

1. Surface epithelial cells secrete mucus and bicarbonate, creating a pH gradient in the mucus layer and change the very acidic gastric lumen to the nearly neutral surface of the mucosa (1).
2. Gastric mucosal cells have a specialized apical surface membrane that resists the diffusion of acid back into the cell.
3. Mucosal cells may directly resist injury by intrinsic mechanisms, such as the extrusion of back-diffused hydrogen ions by means of basolateral carriers (e.g. sodium-hydrogen or sodium bicarbonate exchange) (2).

The rapid repair of injury to mucosa is essential to maintain the mucosal integrity. Surface epithelial cells continually slough, and the gaps are resealed by adjacent cells that move to fill them by cell replication in response to still unknown trophic signals (3). Blood flow in normal mucosa removes the acid that has diffused across a compromised mucosa. Prostaglandins enhance the mucosa's resistance to injury under certain conditions, perhaps by increasing mucosal blood flow (4, 5), stimulating the secretion of mucus and bicarbonate (6), strengthening of the gastric mucosal barrier, decreasing the gastric motility (7), increasing release of endogenous mediators of gastric cytoprotection like sulfhydryls (8) and epidermal growth factor (9) etc., scavenging of free radicals (10), decreasing release of endogenous mediators of gastric injury, vasoactive amines and leukotrienes (11) and stimulation of cellular growth and repair (12).

In general it can be said that there is a plethora of mechanisms underlying the defense of normal gastric mucosa and their relative importance and interdependence is far from clear. This itself may be a pointer that normal gastric defense may be a multifactorial phenomenon.

***Acid secretion and peptic ulcers:***

The formation of peptic ulcers depend critically on the presence of acid and peptic activity in gastric juice. About one third of patients with duodenal ulcer, but not gastric ulcer, secrete excess gastric acid. Schwartz's (13) dictum "no acid - no ulcer" is more accurate if amplified to "no acid and peptic activity - no ulcer" as acid without pepsin has little digestive power. The dependence of peptic activity is supported by the therapeutic effects

of the antacids and antisecretory drugs (anticholinergics, H<sub>2</sub> blockers) and also the antisecretory drug omeprazole which completely inhibits the secretions of acid by blocking the hydrogen-potassium adenosine triphosphatase. However, these ulcers rapidly recur when therapy is stopped, reflecting the non-curative nature of anti-secretory therapy alone.

**Impaired mucosal defense:**

Peptic ulcer is a product of self-digestion; it results from an excess of autopeptic power in gastric juice over the defensive power of gastric and intestinal mucosa (13). The surface epithelial cells of the gastric mucosa have intrinsic barrier property and play an important role in the first line defense of the stomach. Davenport (14) proposed that the apical membrane or tight junctions between epithelial cells are relatively impermeable to hydrogen ions and therefore, forms a physical barrier to back diffusion of acid. He called this the gastric mucosal barrier (14). More recent studies (15) have shown the existence of surface active phospholipids which form the hydrophobic lining on the luminal surface of the gastric epithelium and retard the passage of water soluble ions such as hydrogen ions. Two major factors appear to disrupt mucosal resistance to injury : NSAIDs and *H. pylori* infection. NSAIDs have been shown to eliminate the surface hydrophobicity and disrupt the mucosal barrier to hydrogen ions. The duodenal secretion of bicarbonate is impaired in

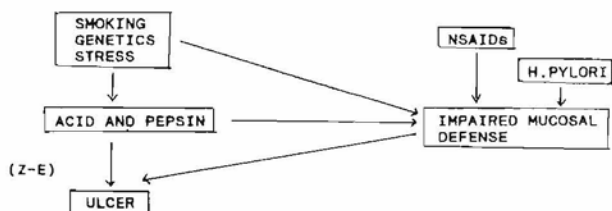


Fig. 1 : A model of the pathogenesis of peptic ulcer.

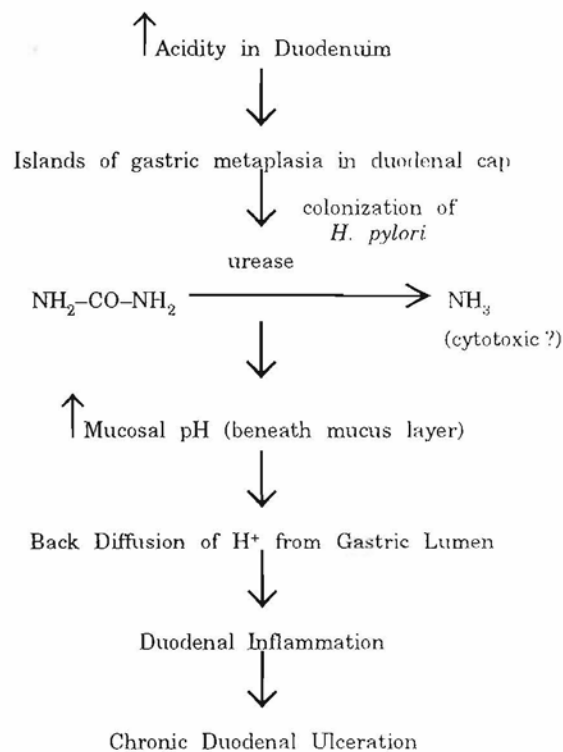


Fig. 2 : Pathogenesis of duodenal ulceration (23).

patients with duodenal ulcer (16), but whether this defect is primary or secondary to other factors, such as *H. pylori*-induced duodenitis or gastric metaplasia, remains uncertain. The production of prostaglandins may be abnormal in persons with peptic ulcer, but no consistent abnormality has been confirmed. On the basis of these considerations, the model depicted in Fig. 1 appears to be more appropriate for the pathogenesis of peptic ulcer than the traditional seasaw model of acid versus mucosal defense.

**Predisposing factors for peptic ulceration:**

*H. pylori* infection :

*H. pylori* induced antral gastritis has been found in nearly all patients with gastric or duodenal ulcer (17, 18). *H. pylori* has been found in the antrum of more than 95 percent of the

patients with duodenal ulcer and in atleast 75 percent of those with gastric ulcer (17,19,20). *H. pylori* is found in the mucus layer or beneath the mucus adhering to gastric epithelium close to the intercellular junctions. Besides its peculiar habitat, *H. pylori* is a very powerful producer of urease and the consequent release of ammonia may provide a microenvironment of raised pH, enabling the organism to survive. Ammonia may be cytotoxic. Electron microscopic studies have shown damage to the gastric epithelial microvilli in the immediate vicinity of *H. pylori* (21). Area of gastric metaplasia, arise in the duodenal cap, possibly associated in some way with high gastric output (22). Colonization of these heterotropic islands with *H. pylori* leads to mucosal injury and subsequent ulceration (23) (Fig. 2).

**Non-steroidal anti-inflammatory drugs:**

NSAIDs produce a spectrum of injury to the gastro-duodenal mucosa, from hemorrhages and petechiae to erosions and ulcers. Major biochemical changes induced by aspirin and other salicylates can be briefly summarized as follows :

- (a) Denaturation of mucus glycoproteins and mucus cell proteins in those areas of the mucosa which are in contact with high concentration of the drug. This leads to sloughing of the protective mucus layer (24), further, discharge of mucus from epithelial cells (25), and cell desquamation. The buffering of the acidic drug or gastric contents to a neutral pH, attenuates these effects,
- (b) Intracellular accumulation of protons dissociated from high concentration of the acidic drug which rapidly accumulate in mucus (superficial) and parietal cells. This causes localized acid accumulation (back-diffusion of acid) (26).
- (c) Labilization of lysosomes in mucosa and parietal cells leading to release of hydrolytic enzymes for cellular autolytic reactions (27).
- (d) Inhibition of PG cyclo-oxygenase, leading to reduced production of PGE (28) and endothelial cell PGI (29). This causes vasoconstriction, inhibition of platelet aggregation (enhanced bleeding), and contributes to the enhanced acid secretion (30).
- (e) Mast cell degranulation results in the release of histamine which stimulates the acid secretion and causes vasodilation. Histamine produces changes in the microvasculature of the mucosa which promotes bleeding from the mucosa.
- (f) Tissue - damaging free radicals which are produced from the conversion of hydroperoxy to hydroxy-fatty acids i.e. HPETE - HETE<sup>+</sup> [O]<sup>-</sup>, further contributes to cell destruction. The hydroperoxy-fatty acids are generated from the following reactions.
  - i) Diversion of arachidonic acid in the lipoxygenase pathway(s) as a consequence of drug-induced inhibition of the PG cyclo-oxygenase pathway (31)
  - ii) Degranulation of mast cells (32).
  - iii) Generalized lipid peroxidation accompanying cell damage.
- g) Inhibition of glucose oxidation (by mitochondria) and inhibition of enzymes involved in anabolic reactions (eg. mucus

synthesis, protein and nucleic acid biosynthesis in regenerating cells). Decreased glucose oxidation leads to reduction in ATP levels which in turn causes reduction in acid secretion, and energy availability required for mucus synthesis. Decreased total ATP levels may also produce stimulation of adenyl cyclase activity and thus increase in cAMP levels (33). The exact significance of this is unclear but may involve regulation of parietal cell acid secretion, regulation of glucolysis and mucus glycoprotein synthesis.

- (h) Stress and drug induced stimulation of corticoid secretion from the adrenal gland could lead to an enhancement of aspirin or other salicylate induced effects as described above. Thus, there could be additive/synergistic effects of both the drug and adrenocortical stimulation on mucus biosynthesis, cellular autolysis, and nucleic acid and protein synthesis, especially in regenerating zones of the mucosa.

#### *Cigarette smoking:*

Gastric and duodenal ulcers occur more frequently in smokers than in non-smokers (34,35). Peptic ulcers heal less well in smoker as compared to non-smokers (36,37). Neither the active tobacco component nor the mechanism by which it operates is known, but, because of its well recognized pharmacological properties, nicotine has been widely investigated as a causative agent (38). Numerous mechanisms have been proposed to explain the effect of smoking on peptic ulcer (39). These include the stimulation of acid secretion (40), alteration of blood flow or motility, induction of bile reflux (41), and reduction in the generation of prostaglandins.

#### *Diet:*

Epidemiological evidence implicates dietary factors in the geographical distribution of duodenal ulceration among people on impoverished diets (42,43), particularly when polished rice forms the main component. In the pylorus ligated rat model (44) an association was demonstrated between gastric ulceration in rats pre-fed with diets corresponding to those areas of India where high and low incidence of human duodenal ulceration are observed (45). In a study in India, people suffering from duodenal ulceration derived symptom relief by supplementation of their diet with fresh rice bran (46,47). This observation was confirmed in the rat model in which fresh rice bran and rice bran oil were found to be protective against ulceration. The protective properties of rice bran and rice oil were lost on storage, when they became actively ulcerogenic. It was considered possible that on storage lipid peroxidation of unsaturated fatty acids in the oil had given rise to the production of cytotoxic ketoaldehydes. Support of this proposal was obtained by the demonstration that cysteine suppressed the ulceration induced by stored rice oil (48).

#### *Psychological stress:*

Stress ulceration of the stomach is associated with clinical conditions like trauma, head injury, burns, shock, sepsis and neurological disorders, and is now regarded as a multifactorial phenomenon. It is reported to result from interactions between mucosal, vascular and neuro-humoral factors, and the autonomic nervous system plays a crucial role (Fig. 3).

Stimulation of gastric mucosa, due to stress is transmitted by cerebral marginal system and hypothalamus to the medulla oblongata and spinal cord. Medulla oblongata stimulates the vagus which increases the gastric secretions and

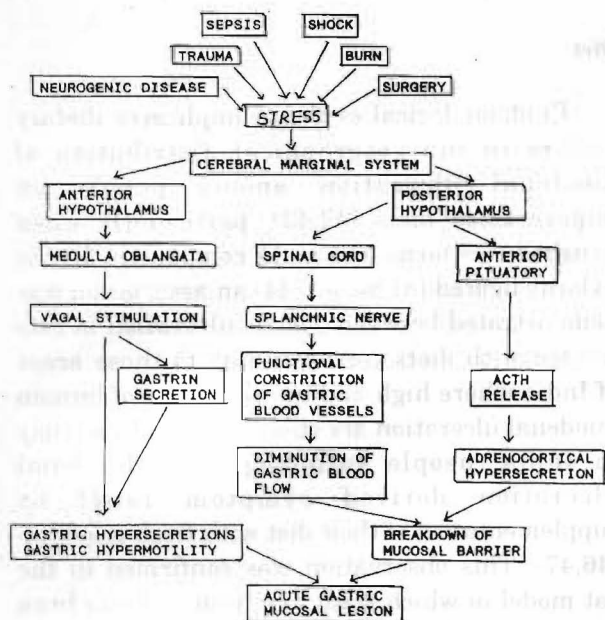


Fig. 3 : Role of the autonomic nervous system in the mechanism causing a peptic ulcer (49).

augments gastric motility. The spinal cord causes the stimulation of the splanchnic nerve to produce a disturbance in circulation due to functional constriction of the gastric vessels; which leads to a diminution of gastric blood flow. The function of anterior pituitary also gets disturbed due to stress releasing adrenocorticotrophic hormone (ACTH) which ultimately leads to increased gastric secretions and reduced gastric mucosal resistance. Circulatory disturbances and the nutritional deficiency, are thus induced in the local tissue, which are then followed by a rapid appearance of a deep ulcer (49).

Electrical stimulation of different regions of the limbic area modulates gastric acid secretion, motility and mucosal blood flow - all of which are important factors for stress ulcer development. The CNS and more importantly, the brain-gut axis are important mediators of stress ulcerogenesis, and complex neural mechanisms

are proposed (50). For example, several disruptive and protective mediators are now recognised, and biogenic amines, aminoacids, and peptides are implicated (51). Neurotransmitters involved in these effects include dopamine, norepinephrine, acetylcholine, gamma-amino butyric acid and several neuropeptides.

#### *Alcohol:*

Ethanol (50-100%) rapidly penetrates the gastric mucosa, and apparently causes cell and plasma membrane damage, that results in increased membrane permeability leading to intracellular accumulation of sodium and water. The "leaky membrane" is a well known stage in the development of cell injury. When the increased membrane permeability fails to maintain the normal electrolyte distribution between intracellular and extracellular compartments, the massive intracellular accumulation of calcium represents a major step in the pathogenesis of gastric mucosal injury. In the gastric mucosa these changes result in cell death and exfoliation in the superficial epithelium, i.e., erosion. Further, gastric lesions caused by ethanol have been attributed to free radical damage, which results in lipid peroxidation products. Clinically, also cirrhosis due to consumption of alcohol is linked to an increased incidence of peptic ulcer (52).

#### *Other diseases and genetic factors:*

Certain diseases such as short bowel syndrome, chronic pancreatitis, Crohn's disease and pulmonary disease (Chronic Obstructive Pulmonary Disease) have also been associated with peptic ulcer. Genetic factors may also be important. Autosomal dominant inheritance of hyperpepsinogenemia I is common in duodenal ulcer, but the nature of causal relations to the pathogenesis of ulcer remains uncertain. Several rare genetic syndromes (Tremor nystagmus ulcer

syndrome, familial amyloidosis, gastrocutaneous syndrome and stiff man syndrome) may also be associated with peptic ulcer (52).

***The changing spectrum of therapy for active peptic ulcer disease:***

***Conventional therapy for the prevention of peptic ulcers:*** Cimetidine and later ranitidine revolutionized the treatment of peptic ulcers, with H<sub>2</sub>-receptor antagonists being the most widely used and effective novel drugs over the past decade. However, relapse ulceration following cessation of treatment with such agents is a frequent clinical observation. It is against this background that we have to deal with the current status and future advances in drug development for the therapy of gastroduodenal ulceration.

***H<sub>2</sub>-receptor antagonists:***

H<sub>2</sub>-receptor antagonists are capable of reducing over 90% of basal, food stimulated, and nocturnal secretion of gastric acid stimulated by histamine, gastrin, cholinomimetic drugs and vagal stimulation (53). Histamine antagonists prevent occurrence of stress induced ulcers. However, their use in combination with antacids may be preferred. In addition, they are important in the medical management of Zollinger Ellison Syndrome and gastric hypersecretory states seen in systemic mastocytosis (54). As described earlier, recurrence of ulcer after healing is a frequent complication of therapy with H<sub>2</sub>-receptor antagonists, and therefore long term treatment is required. H<sub>2</sub>-receptor antagonists are thus remarkable but not perfect drugs. These drugs include mainly cimetidine, ranitidine, famotidine, roxatidine and nizatidine. Saltidine, mifentidine, TZU-0460, CM-57755 etc. are also under investigation and have shown better antiulcer activity (55).

***Ranitidine Bismuth Citrate:*** Ranitidine bismuth citrate (RBC) is the new anti-ulcer drug developed by Glaxo Laboratories (U.K.), which when combined with clarithromycin can eradicate *H. pylori* in 94% of patients. This has been confirmed in a clinical trial on 232 patients with duodenal ulcers. RBC was given 400 mg twice daily for 28 days and clarithromycin four times a day for first 14 days (56).

***Prostaglandins:***

In 1979, Robert (57) recognised that PGs inhibit gastric acid secretion and protect against experimental ulcers caused by NSAIDs, diet and life styles (eg. alcohol, smoking and stress). Misoprostol (Cytotec) is a synthetic prostaglandin E analog with acid reducing and cytoprotective properties. Prostaglandins enhance mechanisms thought to be involved in mucosal defense of the chronic peptic ulcer (e.g., the secretion of mucus, output of bicarbonate, and blood flow) (58). It is indicated for the prevention of NSAID-induced gastric ulceration. Short term co-administration of enprostil lowered the serum gastrin levels in patients on long term treatment with omeprazole (59). Misoprostol does not prevent duodenal ulcer. It is contraindicated in pregnancy because of its abortifacient property and requires special precautions if prescribed to women of child bearing potential. The main side effect is diarrhoea in 6 to 30% of users. The synthetic PGs currently available in market are misoprostol, enprostil, rioprostil, arbaprostil and trimoprostil like compounds. Several other compounds like nocloprost, enisoprost, mexiprost, Nileprost, rosaprostol etc. are undergoing clinical trials.

***H<sup>+</sup>/K<sup>+</sup>-ATPase inhibitors:***

Blockade of the gastric proton pump constitutes a more direct mechanism for acid secretion inhibition compared to blockade of

histamine and cholinergic receptors. Omeprazole is not the active inhibitor of  $H^+K^+$  ATPase enzyme but is reversibly transformed in acidic media to the sulphenamide which can react with thiols to form disulfides, thus representing a model for the covalently linked enzyme-drug complex. Omeprazole has been shown to inhibit the growth of *H. pylori* (60). Recently, lansoprazole has been introduced in the markets of United States of America. NC-1300, RO 18-5362, B831-56 are series of flourinated benzimidazoles and are potent and long acting inhibitors of acid secretion in animals and have shown mechanism similar to that of omeprazole.

#### **Muscarinic receptor antagonists:**

Pirenzepine, a selective muscarinic  $M_1$  receptor antagonists, reduces basal and stimulated acid secretion, in animals and man. Its efficacy in duodenal ulcer is equivalent to cimetidine (61). It has more cytoprotective effect than of histamine receptor antagonists against gastric mucosal lesions induced by ethanol, HCl, NaOH and taurocholate. Telenzepine is 4-10 times more potent than pirenzepine, as an inhibitor of acid secretion in rats and dogs.

#### **Mucosal coating agents:**

**Sucralfate:** Sucralfate is a sulfated disaccharide-basic aluminium sulfate complex. It forms an adherent coating with proteinaceous material at ulcerated mucosal sites. When pH is low, there is extensive polymerization and crosslinking of sucralfate. The coating provides barrier to hydrogen ion diffusion, reduces peptic activity and adsorbs bile salts. Further, sucralfate can bind to both epidermal growth factor (EGF) and fibroblast growth factor (FGF), which also enhance ulcer healing (62). Recently, sucralfate has also been reported to suppress the associated *H. pylori* infection (63).

#### **Bismuth compounds:**

Bismuth subcitrate, formerly called tripotassium dicitrate bismuthate (TDB) is the most recent of the bismuth salts to be tested and found effective clinically. The substance is a colloidal suspension. When the pH is above 3.5 to 4.0; it forms a white precipitate in gastric acid. Bismuth subcitrate has a strong affinity for mucosal glycoproteins, especially in the necrotic tissue in ulcer craters. Ulcer craters become preferentially and visibly coated with a white layer of polymer glycoprotein complex, which is only slowly permeated by  $H_3O^+$ , such that the layer constitutes a diffusion barrier to gastric acid. Bismuth salts also have some antimicrobial activity against *H. pylori* infection. However, the chronic use of other bismuth salts has caused encephalopathy and osteodystrophy (64).

#### **Carbenoxolone:**

It is a synthetic derivative of glycyrrhizic acid (a constituent of liquorice) which has been shown to be of value in promoting healing of peptic ulcers. The mechanism of action is not understood but, is believed to involve an effect on mucus, increasing its secretion and viscosity and thus protecting mucosa from attack by acid and pepsin. Its principal adverse effect is sodium retention which may lead to edema, hypertension and heart failure and this limits its use especially in the old people.(61).

#### **Miscellaneous group:**

The anti-ulcer activity of calcium channel blockers namely verapamil, nifedipine and diltiazem against experimental ulcers has been established (65). Proglumide, a cholecystokinin and gastrin receptor antagonist is also found to possess antisecretory and antiulcer activity (66). The histidine decarboxylase inhibitors like (+) -



cyanidanol-3, naringenin and meciadanol may also be useful in the treatment of peptic ulcer disease (67). FPL 52694, a mast cell stabilizer, has been shown to produce a significant decrease of overnight basal acid in dyspeptic patients after one week treatment (66). Recently, Glavin and Szabo (68,69) have established the role of dopamine in the gastroduodenal disease. In support of above contention, we have reported the anti-ulcer activity of the specific dopamine D<sub>1</sub>-receptor agonists (eg. SKF 38393) and selective dopamine D<sub>2</sub>-receptor antagonists (eg. sulpiride) against selected models of gastric and duodenal ulcers in rats (70, 71).

#### **Treatment of *H. pylori* infection:**

Ultrastructural studies have shown that following an exposure to bismuth preparations *H. pylori* detaches from the gastric epithelium and gets lysed within 30-90 min (72). In spite of the clinical suppression of *H. pylori* with oral bismuth, recrudescence is extremely common following monotherapy with bismuth (73). Therefore, it seems obvious that short term treatment with bismuth alone is inadequate for *H. pylori* infection. Chronic administration of bismuth for the treatment of *H. pylori* is not recommended taking into consideration the risk of bismuth toxicity. In the laboratory *H. pylori* is sensitive to a wide range of anti-microbials including ampicillin, erythromycin, tetracyclines, ciprofloxacin, ofloxacin, metronidazole, tinidazole and nitrofurantion (73). But, monotherapy with antibiotics has been shown to lead to the rapid onset of resistant organisms in some circumstances. Acquired resistance to quinolones has been demonstrated in *H. pylori* after ofloxacin and ciprofloxacin (74). The inadequacy of single agent therapy has led some workers to propose that a combination of bismuth with antibiotics, may provide the optimum approach (75). Combination therapy has provided the best results to date. Eradication rates vary from 40%

with TDB and amoxycillin to 80% with TDB and metronidazole (76). Triple therapy has been found still more effective and 96% of patients will eradicate the organism with TDB, metronidazole and tetracycline (or amoxycillin) combination (75). Further, it is reported that the efficacy of many antibiotics is pH dependent (77). Hence, there is a rationale for combination of acid inhibitory drugs with antibiotics in the treatment of *H. pylori* infection. A controlled study of combination therapy with omeprazole and amoxycillin in patient with duodenal ulcer showed eradication of *H. pylori* in 82% of patients (78). Over the past five years, several workers have suggested that eradication of *H. pylori* significantly reduces the rate of duodenal ulcer relapse (79-80). Recently, National Institute of Health (NIH) Consensus Conference recommended *H. pylori* eradication regimen as the first line medical therapy for patients with peptic ulcer disease who are *H. pylori* positive (81).

#### **Therapy and prevention of NSAID-associated ulcers:**

Ulcers associated with NSAIDs usually heal spontaneously when the NSAIDs are withdrawn. Even with the continued use of NSAIDs, ulcers may heal spontaneously. Limited studies suggest that H<sub>2</sub>-blockers, prostaglandins, and omeprazole accelerate healing as compared to placebo (82, 83). Omeprazole is emerging as the most promising agent for troublesome ulcers, especially when NSAIDs cannot be discontinued (82). A few trials have tested regimens for the prophylactic treatment of NSAID-associated ulceration. A three month trial indicated that misoprostol prevented NSAID-associated gastric ulcer, but data is lacking on the efficacy of PGs in preventing NSAID-associated duodenal ulcer (84). One short term study proved higher efficacy of PGs than H<sub>2</sub>-blockers in preventing NSAID-associated gastric damage whereas H<sub>2</sub>-blockers were effective in preventing duodenal damage (85).

**Treatment of refractory ulcers:**

Regardless of the mode of therapy, the healing of ulcers is time dependent; 90 to 95 percent of all ulcers heal if therapy is continued for 12 weeks. After that, ulcers or symptoms (or both) can be considered refractory to therapy. Since persistent symptoms may not be due to persistent ulcer disease, endoscopy is essential to establish the diagnosis. If persistent ulceration is found on endoscopy, a few possibilities warrant consideration. Poor patient compliance, use of NSAIDs, smoking and gastrinoma are common causes of refractory ulceration. The role of *H. pylori* infection in refractory ulceration also remains uncertain. A 40 mg dose of omeprazole or a full dose antisecretory therapy will probably have to be continued to maintain the healing of refractory ulcers, since it does not alter the natural history of ulcer disease. Treatment with bismuth or the eradication of *H. pylori* (or both) deserves consideration for patients who do not respond to conventional therapy (52).

**Recurrence of duodenal ulcers:**

Duodenal ulcers recur in 70 to 90% of patients within 1 year of the cessation of drug therapy. The evidence suggests that the rate of recurrence differs depending on the initial therapy used.

The relapse rates are higher after healing with H<sub>2</sub>-antagonists as compared to tri-potassium di-citrate bismuthate therapy (86). Maintenance therapy with an H<sub>2</sub>-receptor antagonists reduces this rate to 40%. Patients with complications of recurrence or those taking NSAIDs, and those who have pulmonary, renal or heart diseases are considered to be at a higher risk and should be placed on maintenance therapy to avoid recurrence. A single night time administration of H<sub>2</sub>-antagonist at a dose of one half of the normal therapeutic dose is appropriate. This should be continued for one year. Sucralfate, 1 g at bedtime, is also an effective maintenance regimen. Patients should be then reassessed for further therapy. Patients who have a minimal risk and who experience a recurrence should be reevaluated and reassigned to maintenance therapy. Maintenance therapy is also appropriate for recurrent gastric ulcer, but the response rate may not be as high as that for duodenal ulcer (87).

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