DISSERTATION ON

UPPER GASTROINTESTINAL ENDOSCOPY FINDINGS IN LOWDOSE ASPIRIN CONSUMERS

SUBMITTED FOR

M.D. BRANCH-I (GENERAL MEDICINE)

MARCH 2009

THANJVUR MEDICAL COLLEGE,

THANJAVUR

THE TAMILNADU DR.MG.R.MEDICAL UNIVERSITY, CHENNAI.

FOR THE EXAMINATION IN MARCH 2009

CERTIFICATE

This is to certify that this dissertation entitled "A STUDY ON UPPER GASTROINTESTINAL ENDOSCOPY FINDINGS IN LOW DOSE ASPIRIN CONSUMERS" submitted by Dr.D.RAMACHANDRAN to the faculty of Internal medicine, The Tamilnadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D.Degree Branch-I (Internal Medicine) is a bonafide research work carried out by him under my direct supervision and guidance.

Dr.S.MUTHUKUMARAN,M.D.,
Professor and Head of Department,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur-613004.

Dr.N.JEEVA, M.D.,
Professor of Therapeutics,
Unit Chief,
Thanjavur Medical College,
Thanjavur-613004.

Dr.P.JEYANTHI, M.D.,
The Dean,
Thanjavur Medical College & Hospitals,
Thanjavur-613004.

ACKNOWLEDGEMENT

I gratefully acknowledge and sincerely thank our Dean, Dr.P.JEYANTHI, M.D., Thanjavur Medical College and our former deans Dr.R.M.NATARAJAN, M.S., Dr.S.BALAKRISHANAN, M.D., for having granted permission to do this dissertation in Thanjavur Medical College.

I am immensely grateful to our beloved professor and HOD. Dr. S.MUTHUKUMARAN, M.D., for his guidance and immense support for this study.

It is with deepest appreciation and gratitude that I thank my unit chief, Dr.N.JEEVA,M.D., Prof. of. Therapeutics, my guide and mentor for maneuvering this study at every meander and without whose able guidance, constant encouragement, this study could not have been possible.

I express my sincere gratitude to my beloved former chief Prof. Dr. G.DHANDAPANI,M.D., for his constant guidance and encouragement in my dissertation work.

I am extremely thankful to Prof. Dr.R.GANESAN,MD.,D.M., chief medical gastroenterologist, Dr.C.KRISHNAN,M.D., D.M., medical gastroenterologist for helping and guiding me thorought my dissertation work.

I sincerely extend my gratitude to all the unit chiefs of department of medicine Prof. Dr. S. PALANIYANDY,M.D., Prof .Dr. P.KRISHANAMOORTHY,M.D., Prof.Dr.D.SWAMINATHAN,M.D., Prof.Dr.A.RAJENDRAN,MD., for allowing me to work on their patients in their wards.

I am thankful to our unit Assistant Professors, Dr.P.KUMAR,M.D., Dr.A.SRINIVASAN,M.D., Dr.R.VIVEKSARAVANAN,M.D., Dr.CAESER,M.D., for their guidance and support. I also thank my unit CRRIs for their help in this study.

I will not be pardoned if I am not thankful to the patients who have participated in this study.

CONTENTS

INTRODUCTION

Aspirin is one of the most widely used drug as a anti-platelet agent. Low dose aspirin is the one among the important drugs to be used in management of acute coronary syndrome, acute ischemic stroke. Low dose aspirin has to be taken for life time as a secondary prophylactic measures in coronary artery heart disease, ischemic stroke patients. Currently more than 300 proprietary preparations contain aspirin and the annual consumption is in excess of 20 billion tablets.

Aspirin is most widely studied antiplatelet agent. Its antiplatelet effect is accomplished by acetylating cyclooxygenase enzyme in platelets, thus results in direct inhibition of prostaglandins and thromboxanes from arachidonic acid. This effect is permanent and lasts for the usual 8 day life time of the platelets. Aspirin in doses of 160-325mg daily inhibits the production of thromboxanes A2 in platelets without substantially inhibiting prostacycline formation.

Aspirin is absorbed into gastric mucosal cells where it becomes ionized because of the higher intra cellular pH and damages the cell. The gastro intestinal adverse effects of aspirin are well known for many decades. Aspirin produces dose related GI toxicity. The spectrum of GI morbidity due to aspirin therapy ranges from minor symptoms like nausea, anorexia, to a serious gastro intestinal complications such as peptic ulceration, GI hemorrhage, perforation. Inspite of this, it is widely used, because the benefits out weigh the risks and it is a cheaper drug. Non acetylated salicylates appear to cause a lower incidence of gastro duodenal ulceration than does of aspirin.

Even though there are lot of studies about the gastro duodenal mucosal changes in patients on larger dose aspirin, there are only few studies with low dose aspirin therapy. So we decided to do an endoscopic study in patients on long term low dose aspirin therapy.

AIM OF STUDY

1. To document various types of gastro-duodenal changes of patients on low-dose aspirin therapy endoscopically.

2. To correlate dyspeptic symptoms with endoscopic findings.

3. To know the gastrointestinal safety of low dose aspirin on long term treatment.

REVIEW OF LITERATURE

2.1.1) History of Aspirin [1]:

The use of willow bark and leaves to relieve fever has been attributed to Hippocrates, but was most clearly documented by Rev. Edmund Stone in 1763. Similar properties were attributed to portions from meadow sweet (Spiraea ulmaria), from which the name aspirin is derived.

Salicin was crystallized in 1829 by Leroux and Pina isolated salicylic acid in 1836. In 1859 Kosbe synthesized salicylic acid and by 1874 it was being produced industrially.

In 1899, Hoffman sought to improve the adverse effects profile of salicylic acid. Bayer laboratories in 1899 began testing in animals, the first time that a drug was tested on animals in an industrial setting and proceeded to human studies and the marketing of aspirin. In 1971 Vane discovered that aspirin inhibits PG synthesis and induces GI injury.

2.1.2) Mechanism of action of aspirin [1]:

The principal therapeutic effects of aspirin is inhibition of prostaglandin production. The first enzyme in the prostaglandin pathway is cyclooxygenase. This enzyme converts arachidonic acid (AA) to unstable intermediates PG G2 and PG H2 and leads to the production of thromboxane A2 and other prostaglandins.

There are 2 forms of cyclooxygenase (COX), cyclooxygenase- 1 (COX-1) and COX-2. COX-1 is constitutively found in most normal cells, while cytokines and inflammatory mediators induce COX-2 production (Seibert et al.1997)[2]. COX2 also is constitutively expressed in certain areas of kidney and brain (Breder et al.1995)[3]. and is induced in endothelial cells by laminar shear forces (Topper et al 1996)[4]. Importantly COX-1 is expressed as the dominant, constitutive isoform in gastric epithelial cells and is the major source of cyto protective prostaglandin formation.

(i) Aspirin covalently modifies COX-1 and COX-2, irreversibly inhibiting cyclooxygenase activity.

(ii) This is an important distinction from all NSAIDs because the duration of aspirin's effects is related to the turn over rate of COX in different target tissues

(iii) The importance of enzyme turn over is most notable in platelets, which being anucleate, have a markedly limited capacity for protein synthesis. Thus platelet COX-1 inhibition last for life time of the platelet (3-7 days).

(iv) COXs are configured such that the active site is accessed by the arachidonic acid substrate via a hydrophobic channel. Aspirin acetylates serine 530 of COX-1, located high up in the hydrophobic channel. Interposition of bulky acetyl residue prevents the binding of arachidonic acid to the active site of the enzyme and thus impedes the ability of the enzyme to make prostaglandins. Aspirin acetylates a homologous serine at position 516 in COX-2.

Although covalent modification of COX-2 by aspirin also blocks the cyclooxygenase activity this isoform, an interesting property not shared by

COX-1 is that synthesizes 15(R)- hydroxyl eicosatetraenoic acid, which is metabolized to 15-epilipoxin A4, which has potent anti-inflammatory properties (Serhan and Oliw 2001)[5]. Due to these features, repeated doses of aspirin that actively do not completely inhibit platelet COX-1 derived thromboxane-A2 can exert a cumulative effect with complete blockade.

2.1.3) EFFECTS ON PLATELETS [6]:

In blood platelets COX enzyme inhibition prevents the synthesis of thromboxane A2, a compound which is a vasoconstrictor, causes platelet aggregation and is thus potentially thrombotic.

In blood vessel walls the enzyme inhibition prevents synthesis of prostacyclin, which is a vasodilator, has anti-aggregating properties and is thus potentially thrombotic. Thus aspirin has paradoxical effects.

Duration of these effects however may differ with effects on vascular tissue is shorter than effects on platelets. The difference explained by the vascular cells regain the ability to regenerate prostacyclin in a few hours, but platelets are unable to resynthesise COX.

Inhibition is cumulative on repeated dosage and it has been estimated that daily doses of 20-50mg will result in complete suppression of platelet thromboxane within few days. Large doses of 150 to 300mg can produce maximal suppression almost instaneously.

The unique sensitivity of platelets to inhibition by low doses of aspirin is related to their presystemic inhibition in the portal circulation before aspirin is deacetylated to salicylate on first pass through liver (Pederson and Fitz Gerald 1984)[7].

2.1.4) PHARMCOKINETICS AND PHARMACODYNAMICS[1,8,6]:

Aspirin absorbed rapidly from the gastro intestinal tract when taken orally. Aspirin also be absorbed through skin. After oral dose, absorption of non-ionised aspirin occurs in stomach and intestine.

Peak plasma aspirin concentrations attained within 15-40 minutes following oral administration as aqueous solution or uncoated tablets. Peak plasma salicylate concentrations attained within 30-60 minutes (or) 1.5-2 hrs following administrations of single 650 mg dose as an aqueous solution or as two 325mg uncoated tablets respectively.

After absorption, aspirin is rapidly converted to salicylate. Aspirin begins to acetylate platelets within minutes of reaching presystemic circulation. Aspirin is 80 to 90% protein bound, and undergo hepatic metabolism. At low doses (325mg), elimination is a first order process and serum half life is 3.5hrs. At high aspirin doses the half life increases to 15 to 30 hours because of saturation of hepatic enzymes and zero order kinetics.

2.1.5) THERAPEUTIC USES OF LOW DOSE ASPIRIN[9]:

1. Acute myocardial infarction -160-325mg- as soon as AMI suspected.
2. Unstable angina -75-325mg initially to be given.
3. Angina pectoris- 75-325mg once daily to be continued indefinitely.
4. Chronic stable CAD -75- 162mg daily to be continued indefinitely.
5. Secondary prevention in post-MI/ACS patients -75-325mg OD for life long.
6. Acute ischemic stroke- 160-325 mg initiated within 48hrs of stroke.
7. Secondary prevention of ischemic stroke -50- 325mg daily for life long.
8. Coronary revascularization procedure – CABG, PCI -75-325mg for life long.
9. Atrial fibrillation/ flutter- 150-325mg those with persistent or paroxysmal AF at high risk of stroke.
10. MVPS with unexplained TIAs -50-162mg daily.
11. Carotid end arterectomy -75-162mg initiated pre-operatively and continued indefinitely.
12. Chronic limb ischemia -75-325mg continue indefinitely.
13. Prolonging patency of vascular grafts -75-325mg
14. Acute pericarditis -160-325mg
15. Bioprosthetic heart valves- long term in those in sinus rhythm. -75-100mg.

2.1.6) ADVERSE EFFECTS[10]:

- **Gastro intestinal system:** Abdominal pain, nausea, anorexia, gastric erosion/ulcers, anemia, GI hemorrhage, perforation, diarrhea.
- **Renal:** salt and water retention, edema, worsening of renal function, in renal/cardiac and cirrhotic patients, decreased effect of anti hypertensive medications, decreased urate excretion.
- **CNS:** headache, vertigo, dizziness, confusion, depression, hyperventilation.
- **Platelets:** inhibited platelet activation, propensity for bruising. Increased risk of hemorrhage.
- **Hypersensitivity:** vasomotor rhinitis, angio neurotic edema, asthma, utricaria, flushing, hypotension, shock.
- Vascular closure of ductus arteriosus.

2.1.7) CAUTIONS[9]:

(A) Contraindications:

- Known hypersensitivity to aspirin or any ingredient in the formulation.
- History of asthma, utricaria, or other sensitivity reaction precipitated by other NSAIDs.
- Syndrome of asthma, rhinitis, and nasal polyps.
- Children or adolescents with viral infections (with or without fever) because of possibility with an increased risk of Reye's syndrome.

(B) Warnings/ Precautions:

- Long term alcohol use associated with an increased risk of aspirin induced bleeding.
- It increases bleeding time. These effects important in platelets with inherited (or) acquired bleeding disorder.
- Serious GI toxicity (bleeding, ulceration, perforation) can occur with or without symptoms.
- Avoid highly buffered aspirin preparations in patients with CHF, renal failure or other conditions in which high sodium content would be harmful.
- Renal effects are interstitial nephritis, papillary necrosis, proteinuria, renal failure.
- Pregnancy: use only if clearly needed. Avoid use in 3^{rd} trimester, because of possible premature closure of ductus arteriosus. Avoid 1 week prior to and during labor and delivery.
- Hemorrhagic complications are not observed in low dose aspirin.

2.2) ANATOMY OF STOMACH AND DUODENUM[11]:

2.2.1) Anatomic relationships and divisions:

a. Stomach:

The stomach, a large, distensible bag with the largest diameter of any part of GIT, is located in mid upper abdomen, just beneath the diaphragm. The size and shape vary greatly from person to person, depending upon age, body habitus, posture and interval since eating. Although fixed proximally to esophagus and distally to the duodenum, and by gastro colic and gastro phrenic ligaments, the stomach has great latitude in distension and motion. The full stomach may reach from diaphragm to the pelvic brim.

The stomach abuts many organs. Diaphragm superiorly, the liver and biliary tract to the right, the spleen to the left, and the pancreas, transverse colon posteriorly. The anterior surface of stomach approximates the abdominal wall. Stomach is separated from these organs by peritoneal lining.

Stomach is divided into cardia, a 1 to 2cm segment adjacent to esophago gastric junction, the fundus, the superior part of stomach lying above and slightly posterior to the rest of stomach. The body or corpus, the voluminary portion of stomach, below the fundus, the antrum, the distal region of stomach and finally, the pylorus or pyloric channel, a narrow 1-2cm channel that connects the stomach to duodenum. The shorter right side of stomach is lesser curvature, the opposite longer left side is greater curvature. An intrusion, about two thirds of way along the distal lesser curvature, near junction of body and antrum is incisura angularis.

2.2.1) b) Duodenum:

The tubular, C-shaped duodenum, nestling the head of pancreas, starts at the pylorus and extends to the ligaments of Treitz. The duodenum has no mesentry and in contrast to stomach is largely retro-peritoneal and fixed in position. The first part of duodenum is about 5cm long. The initial 2-3cm of first part is duodenal bulb. The lining of bulb is relatively flat. The second part of duodenum takes a sharp curve and descends along the head of pancreas for 7 to 10cm. The common bile duct and pancreatic ducts together or separately enter the medial aspect of second part at posteromedial ampulla of vater. The accessory pancreatic duct enters the duodenum approximately 2cm proximal to ampulla. The third part passes from right to left across the spine, inclining upward about 5 to 8cm. The fourth part of duodenum starts left of spine, ascends left wards and terminates at ligament of Treitz.

2.2.2) Blood supply:

Gastric and duodenal blood supply derive from celiac artery and the superior mesenteric artery. A dense anastomotic network encircles the stomach is formed by these arteries. The left gastric artery supplies anterior and superior portion of stomach. The right gastric, gastro-duodenal, right gastro epiploic arteries which arise from hepatic artery, supplies lower right portion of stomach and the lower greater curvature. The short gastric and left gastro epiploic arteries arise from splenic artery to feed the fundus and upper greater curvature.

The distal stomach, pylorus, duodenum are supplied by the inferior pancreatico duodenal branch of superior mesenteric artery.

Venous drainage:

Venous drainage from the stomach and duodenum leads directly or indirectly to portal vein. From the stomach, the left and right gastric veins drain the lesser curvature, and the left and right gastro epiploic and short gastric veins drain greater curvature. From duodenum, the anterior inferior and superior pancreatico duodenal veins drain into superior mesenteric vein. The posterior superior pancreatico duodenal veins drains directly into portal vein.

2.2.3) Lymphatic drainage:

The pattern of lymphatic drainage of stomach is similar to that for its vasculature, with most lymph draining ultimately into into celiac nodes via four major groups.

In the duodenum, anterior and posterior lymphatics drain into pancreatico duodenal nodes and to hepatic, pancreatic nodes, then finally into pre aortic nodes near origin of Superior mesenteric artery.

2.3) GASTRIC PHYSIOLOGY[11]:

Gastric Secretion

Two secretory products with the potential of producing mucosal damage include hydrochloric acid and pepsinogen. Basal acid secretion follows a circadian pattern with the lowest secretion in the morning and the greatest occurring at night. Cholinergic input via the vagus nerve and histaminergic input from locally released histamine are the main determinants of basal gastric acid output. The principal physiologic stimulant of increased

acid production is food. Meal-stimulated acid secretion is typically described as occurring in three phases referable to the site of origin of the stimulant and includes the cephalic, gastric, and intestinal phase.

The principal determinants of the cephalic phase include sight, smell, and taste of food, which lead to stimulation of gastric acid secretion via cholinergic input through the vagus nerve. Once food enters the stomach, the gastric phase of acid secretion is activated. Nutrients (amino acids and amines) directly stimulate gastrin release, which in turn increases the secretory response. As nutrients enter the intestine, the last phase of meal-stimulated gastric acid secretion is initiated. The principal stimulatory factors during this phase include distention and proteins and their breakdown products.

As is the case with most biological systems, there are a series of inhibitory pathways that are activated during the different phases of gastric secretion, which serve as a counterbalance for the secretory process. The GI hormone somatostatin seems to be an important element in this inhibitory process.

Extensive effort has been placed towards understanding the cell responsible for secreting acid. The parietal cell is found in the oxyntic gland in close proximity to additional cells involved in regulating acid secretion. One of these cells is the histamine containing enterochromaffin-like (ECL) cell. The ECL cells express receptors for gastrin and acetylcholine. Stimulation of the ECL cell by cholinergic neurons of the enteric nervous system or by the hormone gastrin released from antral G cells stimulates histamine release.

The acid-secreting parietal cell contains receptors for histamine (H2 class), gastrin, and acetylcholine. Activation of the parietal cell H2-receptor

by histamine stimulates adenylate cyclase, increasing intracellular cAMP levels. Stimulation of the cholinergic M3-receptor or the gastrin receptor activates the phosphoinsitide/intracellular calcium cascade.

The increase in intracellular cyclic adenosine monophosphate (cAMP) or cytosolic calcium leads to activation of various protein kinases, which in turn regulate the final common acid-secreting pump on the canalicular surface of the cell: the H^+K^+ATPase.

The combination of secretagogues that activate different signaling pathways leads to a significant increment in gastric secretion. This enhanced biological response is termed potentiation. Potentiation explains why receptor blockade of one pathway with an antagonist diminishes acid secretion in response to agents that activate an alternate pathway.

The H^+K^+ATPase is a membrane-embedded protein that leads to the secretion of H^+. It consists of two subunits: an alpha subunit that contains the active catalytic site; and a beta subunit, the function of which is not fully elucidated. This enzyme uses the chemical energy of ATP to transport protons from the cytoplasm of the parietal cell into the secretory canaliculi in exchange for K^+.

The pumps are located in the secretory canaliculus and in the nonsecreting cytoplasmic tubulovesicles. The distribution of pumps between these locations depends on the degree of parietal cell stimulation. The cytoplasmic vesicles are impermeable to K^+, thus making the proton pump

inactive in this location. In the resting state, approximately 5% of pumps are active and located within the canaliculi.

During stimulation, tubulovesicles of the cytoplasm are rapidly transferred to the membrane of the secretory canaliculus, where 60% to 70% of the pumps are activated. After stimulation of the parietal cell ceases, the proton pumps return to their inactive state in the cytoplasmic vesicles. The half-life of the proton pumps is estimated to be 48 hours.

Pepsinogen, the inactive precursor of the proteolytic enzyme pepsin, is produced by the chief cell, which is found primarily in the gastric fundus. The pathogeneric importance of derangements in pepsinosen secretion in peptic ulcer disease remains to be established.

2.4) GASTRO DUODENAL DEFENSE MECHANISM [11,12]:

The gastric epithelium is under constant assault by endogenous noxious factors such as HCl, pepsinogen/ pepsin, and bile salts. In addition, exogenously substances such as medications, alcohol, bacteria, encounter the gastric mucosa. The mucosal defense system can be envisioned as three level barrier composed of pre-epithelial, epithelial and sub-epithelial elements.

2.3.1) Pre-epithelial defensive factors:

The first line of defense is a mucus- bicarbonate layer which serves as a physico-chemical barrier to multiple molecules including hydrogen ions. Mucus is secreted by surface epithelial cells, which is stimulated by prostaglandins. The thickness of mucus is approximately 100μm. mucus contains 95% water and 5% glycoprotein and lipids. Mucus is a dynamic substance which is continually being secreted and degraded [13]. It functions as non-stirred water layer impending diffusion of ions and molecules such as pepsin. Bicarbonate secreted by surface epithelial cells of gastro duodenal mucosa forms a pH gradient that maintains neutral pH at epithelial cell surface[14].

2.3.2) Epithelial defensive factors:

Surface epithelial cells provide second line of defense through several factors, including mucus production, epithelial cell ionic transporter that maintain intracellular pH, bicarbonate production and intracellular tight junctions. When superficial mucosa damage occurs, surface epithelial cells bordering the site of injury can migrate to restore the damaged area. This is known as restitution [15]. Several growth factors including epidermal growth factor, transforming growth factor α, fibroblast growth factor, modulate the process of restitution. Regeneration, the process by which larger epithelial cell defeats heal, requires cellular proliferation.

MECHANISMS OF GASTRODUODENAL MUCOSAL DEFENSE	
LEVEL OF DEFENSE	MECHANISM OR EFFECT

2.3.3) Sub-epithelial defensive factors:

An elaborate micro-vascular system within gastric submucosal layer is the key component of sub-epithelial defense system, providing HCO**3**, adequate supply of micronutrients and oxygen while removing toxic metabolic by products.

Prostaglandins play a central role in gastric epithelial defense, which regulate the release of mucosal bicarbonate and mucus, inhibit parietal cell secretion, and are important in maintaining mucosal blood flow and epithelial cell restitution.

Nitric oxide (NO) is important in maintainence of gastric mucosal integrity. It contributes cyto protection by stimulating gastric mucus, increasing mucosal blood flow, and maintaining epithelial cell barrier function.

TABLE 2.1

Preepithelial	
Mucus / bicarbonate barrier	Provides a modest barrier to H^+ diffusion and other molecules
Mucoid cap	Develops in response to mucosal injury and provides a juxtamucosal alkaline or neutral microenvironment
Surface-active phospholipids	Enhance hydrophobicity of cell membrane, increase viscosity of surface mucous layer and may affect cell membranes
Epithelial	
Restitution	Prompt reconstitution of surface epithelium by movement of existing cells over damaged area; impeded by ischemia, reduced $Ca2^+$, and acidosis
Cellular resistance	Maintains electrical gradient to prevent epithelial cell acidification, lowered pH1
Acid-base transporters	Transport HCO_3^- into the pH/mucous barrier and subepithelial tissues (i.e., alkaline tide), and extrude acid to prevent cellular acidification
Release of growth factors (e.g., polyamines), prostaglandins, nitric oxide	Growth factors promote cell division; prostaglandins stimulate mucus and HCO_3^- secretion and increase mucosal blood flow; nitric oxide increases mucosal blood flow
Subepithelial	
Mucosal blood flow	Delivers nutrients and buffers, especially HCO_3^-, to the surface epithelial cells
Leukocyte adhesion and extravasation	Neutrophil endothelial adherence and their extravasation into the submucosal tissues with the release of cytokines and the generation of oxygen-derived free radicals are important factors in experimental mucosal injury.

2.5) ABNORMALITIES ASSOCIATED WITH PEPTIC ULCER[16]:

Reported abnormalities in gastric acid secretion, acid homeostasis, and gastro duodenal motility that are associated with peptic ulcer disease are reviewed in this section. Consequently, clinical investigations on peptic ulcer conducted before 1984 do not even consider the H. pylori status of the study population. Although this infection is found in more than 80% of patients with duodenal ulcer and in more than 60% of patients with gastric ulcer, the precise contribution of H. pylori to a number of the physiologic abnormalities described in peptic ulcer disease remains unclear.

2.5.1) ABNORMALITIES ASSOCIATED WITH DUODENAL ULCER:

Numerous studies have concluded that patients with duodenal ulcer disease tend to be hyper secretors of gastric acid. Autopsy studies have shown that groups of duodenal ulcer patients have greater mean numbers of gastric parietal cells than groups of control subjects without peptic ulcers, although much overlap is observed between these groups The average maximal and peak acid outputs (which correlate with parietal cell mass) and the mean duration of meal-stimulated acid secretion also are greater in patients with duodenal ulcer than in control subjects, again with considerable overlap among individuals within the groups, Similarly, basal acid output, daytime acid output, and nocturnal acid output are, on average, increased in patients with duodenal ulcer compared with control subjects without peptic ulcer disease The abnormality in nocturnal gastric acid secretion may be particularly important because during sleep, when there is no food in the stomach to buffer gastric acid, the gastro duodenal mucosa may be especially susceptible to peptic injury,

Abnormalities in the homeostatic mechanisms that regulate gastric acid output may contribute to the acid hypersecretion found in some patients with duodenal ulcer. For example, fasting serum gastrin levels are higher in duodenal ulcer patients than in normal control subjects. Meal- and gastrin-releasing peptide-stimulated gastrin levels are also higher in H.pylori infected duodenal ulcer patients than in uninfected normal control subjects, but these levels in ulcer patients are no higher than those of control subjects with H.pylori infection who are otherwise normal. In some cases the gastrin abnormalities associated with duodenal ulcer are reversible with eradication of H. pylori infection. The precise mechanisms underlying the aberrant gastrin secretion found in duodenal ulcer disease are not clear but may involve H. pylori-induced increases in cytokines such as tumor necrosis factor-a that stimulate gastrin release from G cells and H.pylori mediated decreases in the mucosal expression of somatostatin, a peptide that normally suppresses gastrin release. This decrease in mucosal somatostatin may underlie the impaired inhibition of acid secretion in response to antral distention and antral acid secretion that has been described in some patients with duodenal ulcer disease.

Serum concentrations of pepsinogen I, a protease made by chief and mucous neck cells in the gastric oxyntic mucosa, are elevated in up to 50% of patients with duodenal ulcers. This phenomenon may reflect the increased gastric secretory mass of patients who have duodenal ulcers. Although once regarded as a genetic marker for duodenal ulcer disease, hyperpepsinogenemia appears to be another reversible consequence of H.pylori infection of the stomach. Abnormalities in the vagal control of acid

secretion have been postulated in some duodenal ulcer patients. These patients exhibit a dramatic decrease in acid secretion after vagotomy or atropine administration. In some patients who have basal acid hypersecretion, sham feeding (which activates vagal efferent pathways to the stomach) does not cause a further increase in acid output. In these patients the basal acid persecretion appears to be driven by increased basal vagal tone that cannot be augmented by sham feeding. One report has suggested that the vagus nerves may even be larger in duodenal ulcer patients than in control subjects without ulcers.

An increased rate of gastric emptying for liquids has been described in some patients with duodenal ulcer disease. Conceivably, rapid emptying of gastric acid into a vulnerable duodenum might predispose to ulceration. Compared with normal individuals, furthermore, patients with active duodenal ulcer exhibit a significant decrease in bicarbonate production by the proximal duodenum, This phenomenon also might predispose to add-peptic injury in the duodenum. Foci of gastric metaplasia are found in the duodenal bulb of most patients with duodenal ulcer. Whereas H. pylori can infect gastric, but not intestinal, mucosa, it has been proposed that these islands of infected gastric tissue in the duodenal bulb may be especially susceptible to peptic ulceration. Some investigators have found a higher prevalence of gastric metaplasia in the proximal duodenum of patients with duodenal ulcer disease compared with healthy control subjects, whereas others have failed to confirm an association between duodenal gastric metaplasia and duodenal ulceration. Consequently, the role of duodenal gastric metaplasia in duodenal ulcer disease remains unclear.

An increased acid load in the duodenum may predispose to ulceration directly, through the caustic effects of acid on the duodenal epithelium, and indirectly, through mechanisms involving H. pylori. The growth of H. pylori is inhibited by bile acids that are present in duodenal juice. Acid can precipitate bile acids, an effect that might allow H.pylori to proliferate and contribute to ulceration in the duodenum.

2.5.2) ABNORMALITIES ASSOCIATED WITH GASTRIC ULCER

The gastric antrum normally is lined by a columnar epithelium that does not secrete acid, whereas an acid secreting (oxyntic) mucosa with abundant parietal cells lines the gastric body and fundus. The large majority of gastric ulcers occur in the non-acid-secreting epithelium at or near its junction with oxyntic mucosa, a phenomenon suggesting that the non-acid-secreting epithelium is inherently more susceptible to peptic ulceration. Long-standing gastritis, as occurs in H. pylori infection can cause atrophy of the oxyntic mucosa, with the development of intestinal metaplasia and the extension of a non-acid-secreting type of epithelium into the proximal stomach.

Patients who have ulcers located in the proximal stomach usually have chronic gastritis and substantial gastric atrophy. Not surprisingly, therefore, peptic ulcer disease that involves only the body and fundus of the stomach (type I gastric ulceration) has been found to be associated with hyposecretion of gastric acid, with a low-normal parietal cell mass and a decreased maximal acid output. Serum levels of pepsinogen II, a protease found in antral, as well as oxyntic, mucosa are elevated in patients with type I gastric ulcers.

In contrast, patients who have concomitant ulcers of the gastric body and the duodenum (type II gastric ulceration) and patients who have gastric ulcers confined to the prepyloric antrum (type III gastric ulceration) have abnormalities in gastric acid homeostasis similar to those of patients with duodenal ulcer disease, often with elevated levels of pepsinogen.

It has been proposed that the reflux of noxious material from the duodenum into the stomach may contribute to gastric ulceration in some patients. Potentially damaging agents in duodenal juice include bile salts and lysolecithin, and increased amounts of these agents have been found in the stomachs of patients with gastric ulcers. Decreased pyloric sphincter pressures have been found in patients with gastric ulcer, a phenomenon that might predispose to duodenogastric reflux.

Antral motility abnormalities and abnormalities in the gastric emptying of solids also have been associated with gastric ulceration in some patients. The importance of any of these abnormalities in the pathogenesis of peptic ulcers remains unclear, and it is known whether the observed motility abnormalities are primary defects or secondary effects of gastric ulceration.

Table 2.2

Reported Abnormalities in Gastric Acid Secretion and Homeostasis in Peptic Ulcer Disease.

Duodenal Ulcer

Increased:

Gastric parietal cell mass

Maximal acid output

Peak acid output stimulated by meals

Duration of meal-stimulated acid secretion

Basal acid output

Daytime acid output

Nocturnal acid output

Fasting serum gastrin levels

Meal- and GRP-stimulated gastrin levels

Serum concentrations of pepsinogen I

Rate of gastric emptying for liquids

Decreased:

Bicarbonate production by the proximal duodenum

Gastric Ulcer

Increased:

Serum levels of pepsinogen II

Duodenogastric reflux

Decreased:

Gastric parietal cell mass

Maximal acid output

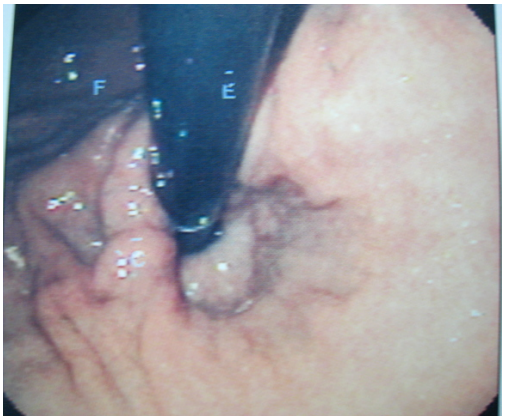
2.6) Endoscopic appearance of stomach and duodenum[17]:

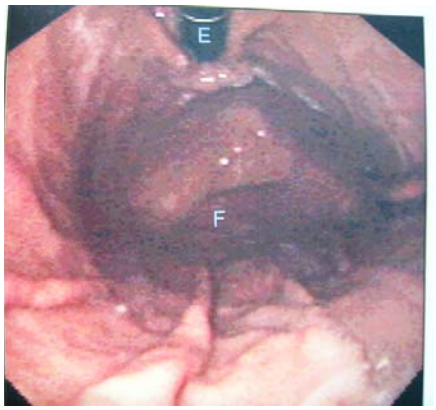
2.6.1) Esophagus:

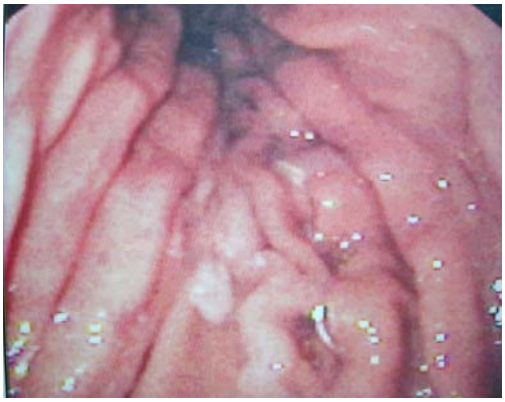
Esophagus can be inspected in details on either the insertion or removal of the endoscope. The upper esophageal sphincter is a high pressure zone 2-3cm in length formed by the crico-pharyngeus muscle. The striated, skeletal muscle of proximal esophagus transitions gradually to the smooth muscle of distal esophagus. The lower esophageal sphincter is tonically contracted to prevent reflux of gastric contents and relaxes with swallowing. The squamocolumnar junction is junction of white stratified, squamous epithelium of esophagus and the salmon colored columnar epithelium of gstric cardia. The squamo-columnar junction is normally located within the zone of lower esophageal sphincter. The gastro esophageal junction is defined as the proximal end of gstric folds. The third landmark of distal esophagus is diaphragmatic impressions.

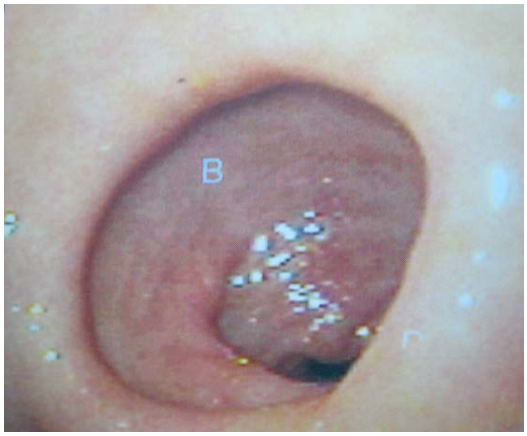
2.6.2) Stomach:

After entering stomach, the pylorus, antrum, incisura angularis are inspected. Retro-flexion is routinely performed in the stomach to allow inspection of lesser curvature, cardia, fundus.



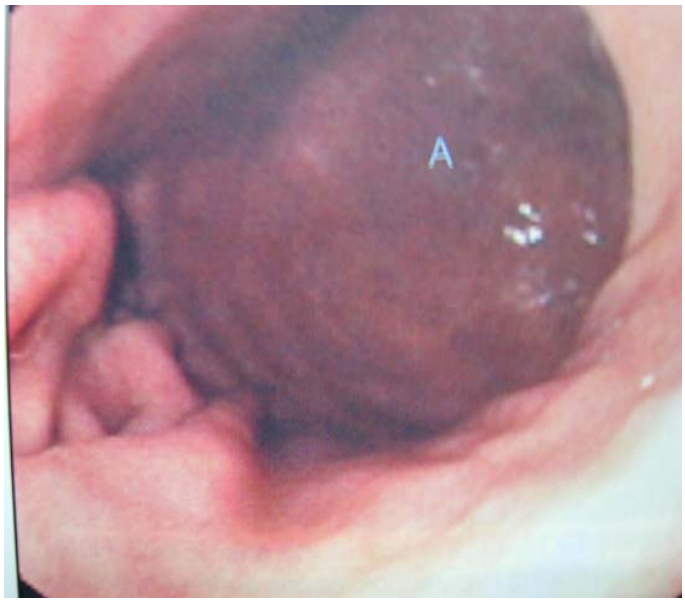






2.6.3) Duodenum:

Once pylorus is passed, the duodenal bulb is inspected in detail on entry. Passing the superior duodenal angle sometimes requires blind maneuver and lesions in this area can be difficult to appreciate. The second part of duodenum is examined for atleast partial visualization of ampulla of vater.



2.7) EFFECTS OF ASPIRIN ON GASTRO INTESTINAL TRACT[6]:

Clinical and epidemiological studies suggests that aspirin produces dose related GI toxicity. Meta analysis suggests that the risk of gastro intestinal bleeding is not significantly lowered with low dose aspirin (less than 300mg daily)[19]. Gastric injury occurs even with doses of 10mg daily. Comparative studies of acute gastric mucosal damage by NSAIDs consistently associate aspirin with most severe lesions. Gastric mucosal injury can occur with even cutaneous application.

Aspirin related gastro intestinal damage is not limited to the stomach and duodenum as these agents also causes injury through the length of GIT.

2.7.1) Pathogenesis of aspirin induced GI toxicity[11]:

The pathophysiology of aspirin induced injury can be grouped into two categories. Those dependent on inhibiton of enzyme COX and those independent of COX inhibition[16].

a) Topical damage:

Topical effects of aspirin is the likely major mechanism responsible for acute hemorrhage and erosions. Aspirin is a weak organic acid and soluble at gastric pH[20]. In strongly acid environment of gastric juice (pH<2.5), aspirin is non-ionised and freely diffuse into mucosal cell cytoplasm, where they ionize at neutral pH and thus become trapped within cells. The high intracellular drug causes local toxic effects. These toxic effects lead to abnormal ion flux across epithelium, with increase H+ back diffusion, one mechanisms of local effect is an uncoupling of oxidative phosphorylation, resulting in mitochondrial energy production, a reduction in cellular integrity, and increase in cellular permeability[21]. Another mechanism is an attenuation of phospholipids content and surface hydrophobicity of the gastric mucus gel layer[22].

Even 10mg of aspirin significantly reduces the gastric mucosal PGs to 40 % of basal levels. 10mg, 81mg, 325 mg, aspirin produces gastric injury and only 325 mg produces duodenal injury. 325 mg per day aspirin reduces duodenal mucosal PGs to 40 %.

b) Systemic effects[16]:

COX is the rate limiting enzyme in prostaglandin synthesis is systemically inhibited by aspirin and is the major mechanism of GI toxicity. Aspirin by acetylation of cyclo oxygenase inhibits this enzyme irreversibly. As little as 10mg aspirin suppress gastric prostaglandin by approximately 60% and can cause gastric ulcers. After low daily doses of aspirin, prostaglandins do not fully recover in stomach approximately 5 to 8days.

Although COX inhibition clearly plays an important role in mucosal injury, other effects probably contribute to the injury. After aspirin administration, gastric acid secretion increases, gastric mucosal flow decreases, and duodenal bicarbonate increases and gastrointestinal mucus secretion decreases. Among these reduction in gastrointestinal blood flow is probably major contributor.

2.8) RISK FACTOR FOR ASPIRIN INDUCED GI TOXICITY[16]:

Certain groups of aspirin taking patient appear to be at greater risk of development of ulcers and should be given greater consideration for strategies to prevent or reduce ulceration.

Definite risk factors are prior peptic ulcer disease, advanced age, prior NSAID induced gastro intestinal complication, concomitant use of glucocorticoids, anti-coagulants, combinations of NSAIDs, comorbid disease, ethanol use.

Possible risk factors are H.pylori infection, smoking.

2.8.1) Old age:

Elderly patients are particularly prone to develop aspirin induced GI toxicity and unfortunately they are most frequent users of this group of drugs. (yeoman, 2001)[23]. The elderly patients are deficient in cyto protective prostaglandins (PGE2 and PGI2) that increase mucus production and improve ulcer healing. Moreover the vascular integrity of the ulcer base is poor. Therefore ulcer bleed easily in elderly patients (Dhikav, 2001)[24]. Elderly patients usually have painless gastric ulcerations and NSIAD can mask the symptom of pain. Elderly are at the greatest risk for drug induced GI bleeding and relative risk at 65-74 year age group is 3-8 times that in general population. (Griffin et al, 1991)[25].

2.8.2) Chronic drug intake:

Chronic low dose aspirin therapy (150mg/day) for conditions such as cardiovascular prophylaxis causes substantial GI toxicity and patients may present with iron deficiency anemia, as chronic use of aspirin can cause upto 2 litres of blood loss over years (Andre[26] et al, 1999, yeoman et al 2001). The risk of bleeding increases with incremental doses of NSAIDs (Singh, 1999)[27].

2.8.3) Use of gastro-protective agents:

Gastro-protective agents are often co-prescribed with low dose aspirin, with an aim to reduce the associated GI adverse effects. Co-prescribing rates range from 17 to 34% in literature (Rogind, 1997)[28].

Studies have found significant interactions (P<0.001) between ulcer healing drugs and NSAIDs. All the interactions were less than 1.0, indicating that the risk of adverse gastro intestinal events associated with taking aspirin is low in patients also taking ulcer healing drugs that in patients not taking ulcer healing drugs (Hooper et al 2004)[29].

The most commonly used gastro protective agents include proton pump inhibitor, H2 receptor antagonists, antacids, and misoprostol. Although these agents have shown to be efficacious to certain extent in prophylaxis and treatment of NSAID related events. Parentral PPI are most efficacious of all gastro protective drugs. Misoprostol has shown to reduce the serious upper GI complications by almost 40%, but is poorly tolerated because of its own side effects, mainly diarrhea and abdominal pain.

2.8.4) Known PUD:

Patients with previous history of complicated or un-complicated ulcers are reported to have the highest absolute risk (around 38.5%) for UGI bleeding (Lucker et al, 1994)[30]. The VIGOR study (Paulsen et al, 1991)[31] involving over 8000 patients has reported the relative risk of having a GI event as 4.0 for patients with prior UGI events. Patients with past history of PUD are having highest risk to develop aspirin induced ulcer and bleeding.

2.8.5) Smoking:

Smoking increases acid secretion, reduces prostaglandin and bicarbonate production, accelerates gastric emptying and decreases mucosal blood flow, all favouring ulcerogenesis. It is suggested atleast in men , chronic smoking increases maximal gastric secretion, and therefore could have a role in the etiology of duodenal ulcer. Smoking is found to be associated with a three fold elevation in the risk of UGI bleed in patients on aspirin compared with no smoking (Peura, 2004)[32]. Ulcer healing with H2 receptor antagonist is significantly delayed in smokers compared to non-smokers. Also the relapse rate of duodenal ulcer is higher in smokers compared with non-smokers.

2.8.6) Concomitant use of other gastro toxic drugs:

Glucocorticoids lead to atrophy of all epithelial tissues including gastrointestinal mucosa. Their rloe in ulcerogenesis is relatively small. Hemorrhage in steroid takers is related to duration of therapy and dose. Although hemorrhage seems to be the mostimportant complication from peptic ulcers in steroid treated patients, gastro duodenal perforation is also a well recognized complication attributed to use of cortico steroids leading to peritonitis. Anticoagulants do not cause UGI bleeding per se, but they can mask or aggravate hemorrhage from pre-existing lesions (Dalton et al, 2003)[33]. Steroids and anticoagulants when combined with low dose aspirin, they increase the chance of UGI bleeding many folds.

2.8.7) Alcoholism:

Regular alcohol consumption combined with regular aspirin use is an additive risk factor for serious upper GI adverse effects. Regular use of lower doses of aspirin increases upper GI risk in those frequently consuming alcohol. Among current drinkers, aspirin taken atleast every other day at dose of 325mg/day or greater is associated with a seven fold increased risk of UGI bleeding when compared with those who do not drink or use low dose aspirin.

2.8.8) H. pylori infection:

Aspirin use and H.pylori infection is regarded as independent risk factors for peptic ulcer disease. NSAID users infected with H.pylori have an almost two fold increased risk of developing bleeding peptic ulcers compared with uninfected NSAID users and low dose aspirin causes more gastric injury in H.pylori infected subjects than in uninfected persons. Eradication of H.pylori is indicated for patients with identified peptic ulcers, regardless of NSAID use. There may be a synergistic injury GI effect between aspirin and H.pylori and high risk patients taking aspirin will benefit from H.pylori eradication.

2.9) ENDOSCOPIC APPEARANCE AND CLINICAL FEATURES OF ASPIRIN INDUCED GI TOXICITY:

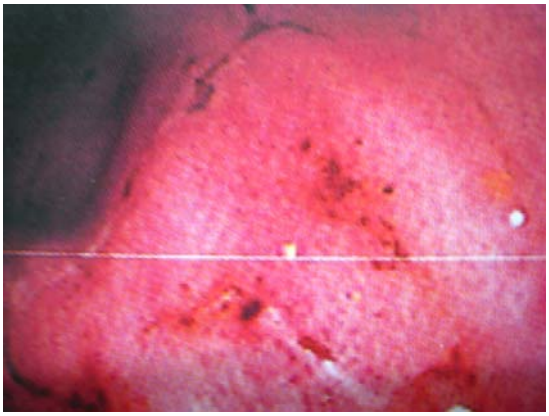
The first endoscopic evidence of adverse effects of aspirin may be reported in 1939 by Douthwaite and Lintoff. NSAIDs induced GI damage are three main types:

1. superficial damage such as mucosal hemorrhage and erosions.
2. Endoscopically documented asymptomatic ulcer.
3. Symptomatic ulcer causing complication such as GI hemorrhage.

2.9.1) Superficial lesions[11]:

Sub-epithelial petechiae are hemorrhages and erosions may be seen with acute and chronic aspirin ingestion.

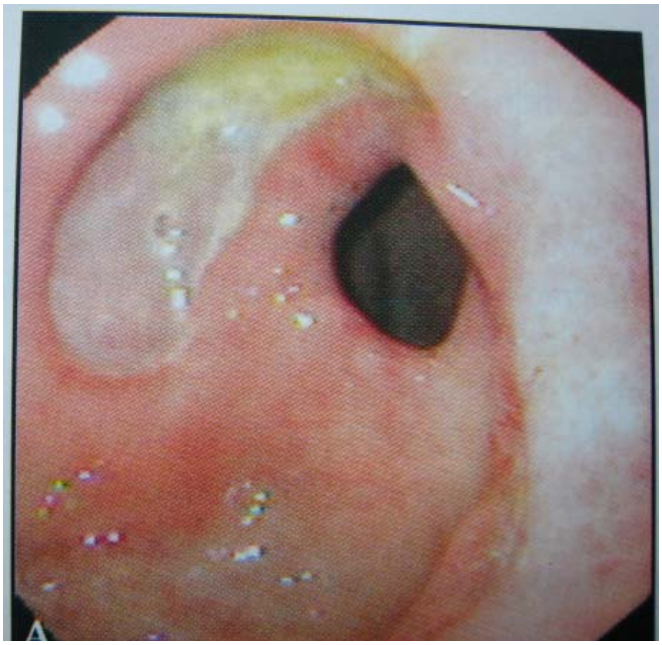
Within one hour of ingesting a single dose of aspirin multiple sub-epithelial hemorrhages are seen in stomach especially in fundus. Repeated dose of aspirin over a period of 24 hours leads to gastric erosions predominantly in the antrum. If aspirin is continued for several days petechiae and erosions become less prominent, a process known as gastric adaptation. Despite adaptation gastric erosions are found by endoscopy in 30 to 50% of patients on chronic NSAIDs.



2.9.2) Ulcers[11]:

Chronic aspirin ingestion causes gastro duodenal ulceration. Aspirin ulcers are usually symptomless unless it is complicated. Early symptoms are mild and benign like dyspepsia, nausea, vomiting and anorexia. Pain is usually a late feature. When ulcer starts bleeding, hemetemesis and malena occurs in 1 to 3% patients (Vikas et al, 2003)[34]. Elderly patients usually have painless gastric ulceration and NSAIDs can mask the symptoms of pain.

Thus the gastric response to the continuous aspirin injury is to heal and to do so at an accelerated rate. This compensatory adaptation is not invariable and delayed healing occurs in some patients and there is definite association between chronic aspirin ingestion and chronic gastric ulcers.



FEATURES OF ASPIRIN INDUCED GI ulcer:

1. More than 3mm in size
2. deep lesions, prone to complications like bleding
3. perforations
4. obstructions
5. multiple erosions (more than 10)
6. antral in location
7. absence of H.pylori

Table 2.3: Effects of Aspirin on upper GI tract:

Injury Type	Gastroduodenal Lesions	Frequency
Acute (1-2 weeks)	Multiply Erythema, Superficial Erosions, Submucosal Haemorrhages, Focal Blood Loss	60 – 100 %
Chronic (> 4 weeks)	Gastric, Antral Erosions, Gastric ulcer, Duodenal Ulcer and Erosions	5 - 30 %

2.10) Ulcer Complications[11]:

Complications of peptic ulcer disease include hemorrhage, perforation, penetration, and obstruction. Intractability, previously considered a complication of ulcer disease, is exceedingly rare subsequent to the development of more effective antiulcer drugs (e.g., H^+K^+ATPase inhibitors).

2.10.1) Hemorrhage:

Hemorrhage, the most common complication of ulcer disease, occurs in approximately 15% of patients. Although ulcer hemorrhage may occur at any age, it tends to be more common in patients during the sixth decade of life and beyond. The higher bleeding rates are in large part due to the increased use of NSAIDs. Approximately 10% to 20% of patients bleed from a gastric or duodenal ulcer without any antecedent symptoms. Approximately one third of patients treated with traditional ulcer therapy (e.g., H2 receptor antagonists) have recurrent hemorrhage. Studies suggest that eradication of H pylori prevents duodenal ulcer and non-NSAID gastric ulcer recurrences and may prevent recurrent hemorrhage.

2.10.2) Perforation:

Ulcer-related perforation is less common than hemorrhage but more common than obstruction, occurring in approximately 7% of patients with peptic ulcer disease. Duodenal ulcers tend to perforate anteriorly, and gastric ulcers tend to perforate along the anterior wall of the lesser curvature of the stomach. With the increased use of NSAIDs, the incidence of perforation is increasing, particularly in women, older than 60 years of age.

2.10.3) Penetration:

Penetration is similar pathologically to perforation, except that the ulcer crater burrows through the entire wall of the intestine, and instead of leaking digestive contents into the peritoneal cavity, the crater bores into an adjacent organ. Gastric ulcers most commonly penetrate into the left lobe of the liver, while duodenal ulcers penetrate posteriorly into the adjacent pancreas, sometimes leading to pancreatitis. Rarely, gastric ulcers may penetrate into the colon, resulting in a gastrocolic fistula.

2.10.4) Gastric Outlet Obstruction:

Gastric outlet obstruction, also referred to as gastric retention or pyloric stenosis, can result from functional impairment of antral motility due to the effects of acute inflammation and edema, or from mechanical obstruction due to scarring near the gastro duodenal junction. The former tends to resolve with medical treatment, and the latter usually requires surgical or endoscopic (i.e., balloon dilation) intervention. The prevalence of gastric retention is approximately 2% in patients with peptic ulcer disease. The symptoms of gastric outlet obstruction tend to be insidious and can manifest as gastroesophageal reflux, early satiety, weight loss, abdominal pain, and vomiting. As the degree of retention increases, the quantity of vomitus also increases, often containing food ingested 12 or more hours previously.

2.11) TREATMENT:

2.11.1) Treatment of NSAID related dyspepsia:

a) H2 blockers:

Dyspeptic symptoms are commonly reported by patients taking aspirin. In a prospective double blind European study 127 symptomatic individuals using NSAIDs without significant abnormalities were randomized to treatment with either cimetidine 400mgs twice daily or placebo. 95% patients had upper abdominal pain, 60% had nausea, and 75% had heart burn, while only 49% of those receiving placebo reported resolution of their symptoms, 72% of those receiving cimetidine reported complete symptomatic remission[35].

Vangroenendael[36] et al investigated efficacy of ranitidine 150mg twice daily in treating NSAIDs related dyspeptic symptoms. Among those without

endoscopic of any mucosal damage, only 6% and 26% patients treated with placebo and ranitidine respectively had complete disappearance of their dyspeptic symptoms.

b) Proton pump inhibitors[38]:

In a study by EkStrom[37], patients with no or mild dyspepsia and with a need for continuous NSAID treatment were randomized to receive either 20mg omeprazole once daily or placebo. Gastro duodenal ulcers, erosions, dyspeptic symptoms were evaluated after 1 and 3 months. The development of moderate to severe dyspepsia requiring active treatment, either alone or in combination with ulcers or erosions occur in 15.3% patients treated with omeprazole and 35.6% of those who received placebo.

A double blind trial comparing omeprazole 20mg once daily and ranitidine 150mg twice daily in NSAID users demonstrate that omeprazole was significantly more effective than ranitidine in decreasing the incidence of dyspepsia.

The role of anti-secretory therapy for treatment of upper GI symptoms in patients receiving low dose aspirin is less clear. In a double blind trial when compared with placebo PPI significantly reduces heart burn but not other aspirin associated symptoms.

2.11.2) TREATMENT OF ACUTE ASPIRIN RELATED GASTRO DUODENAL ULCERS[16]:

A) H2 receptor antagonist:

Current evidence suggest that conventional doses of H2 receptor antagonist effectively heal duodenal ulcer but are ineffective for gastric ulcer. In a multi-center study gastric ulcer heal in 63% of those taking NSAID

compared with 95% of those who had stopped. At 12 weeks 79% of gastric ulcers and 92% of duodenal ulcers were healed in group continuing NSAIDs whereas GI ulcers healed in those who had stopped taking NSAIDs.

B) Proton pump inhibitors:

Current evidence indicate that PPI is superior to standard dose H2 receptor antagonist therapy in healing NSAID associated ulcers. In a study comparison of 20mg and 40mg omeprazole and ranitidine 150mg (twice daily), in patients who continued to take NSAIDs, ulcer healing at 8 weeks was found in 805 of patients given omeprazole 20mg daily, in 79% of those given omeprazole 40mg daily but in only 63% of those given ranitidine 150mg twice daily.

C) Misoprostol:

Prostaglandin exert their therapeutic effect both by enhancing mucosal defensive properties inherent to gastro duodenal mucosa and by inhibiting acid secretion, while protective effect is observed with all doses of Prostaglandin, acid secretion affected only with higher doses. Misoprostol role in NSAID associated ulcer is less studied. One large scale randomized trial compare misoprostol 200µg four times daily with omeprazole 20 or 40mg daily in patients who continued NSAID treatment. After 8 weeks duodenal ulcers healed in 89% patients receiving either doses of omeprazole and 77% of those receiving misoprostol. Gastric ulcer healed in 80% of those receiving 40mg omeprazole, in 87% of those receiving 20mg omeprazole and in 73% of those receiving misoprostol.

2.12) Prophylaxis[12]:

Individuals who are not at risk for cardio vascular events, do not use aspirin and are without risk of GI complication can receive non-selective NSAIDs without gastric protection. In those without cardio vascular risks for GI complication but with high potential risk for NSAID induced GI toxicity, cautious use of selective COX-2 inhibitors or NSAID with gastric protection with PPI is order.

Patients with cardiovascular risk factors who are on low dose aspirin and have low potential for NSAID induced toxicity should be considered for a non NSAID agent or use of traditional NSAID in combination with gastric protection. Patients with cardiovascular and GI risk who require aspirin must be considered for non-NSAID agent.

MATERIALS AND METHODS:

4.1 Materials & Methods:

Place of study:	Thanjavur Medical College Hospital , Thanjavur
Type of study:	Observational study
Period of study:	December 2007 to November 2008
Collaborating Department:	Medical Gastro Enterology
Consent:	Informed & Written consent obtained

4.2 Selection of Patients:

Known CAHD patients already on drugs admitted in medical ward, CAHD patients who were registered in cardiology, diabetology, neurology clinics and on drugs, periodic follow up were included in this study.

The study was conducted during December 2007 to November 2008.

4.2.1 Inclusion Criteria:

1. Patients who were on low dose aspirin (150 mg per day) for at least 6 months
2. Both symptomatic and asymptomatic individuals
3. Patients on gastroprotective agents and not on gastroprotective drugs

4.2.2 Exclusion Criteria:

The following class of patients were excluded from this study

1. Patients on less than 6 months of aspirin treatment
2. Patients with cardiac arrythimas

3. Patients with severe LV dysfunction
4. Acute coronary syndrome patients
5. Poor general condition
6. Known case of peptic ulcer disease on treatment
7. Patients who were on high dose aspirin

4.3 Study Methods:

Patients who were on low dose aspirin (150 mg per day) for at least 6 months were selected randomly. There was no age limit for this study. Detailed history was taken and thorough physical examination was made.

4.3.1 History:

All patients were asked about

1. History of dyspeptic symptoms like indigestion, Anorexia, Nausea etc.
2. History of UGI bleed like Hematemesis, Melena.
3. History of upper abdominal pain.
4. History of Smoking and Alcoholism.
5. History of other ulcerogenic drugs like other NSAIDs, corticosteroids.
6. History of Gastro protective agents like H2 receptor antagonists, proton pump inhibitors, along with aspirin.
7. Duration of low dose aspirin.
8. Past history of upper GI symptoms and peptic ulcer disease.
9. Treatment history for dyspeptic symptoms.

4.3.2 Physical Examination:

1. General condition, anaemia, pulse, blood pressure were recorded.

2. All systems including abdomen, CVS, respiratory system, nervous system were examined and findings noted.

4.3.3 Consent :

Informed consent was obtained from all the patients after explaining the procedure and risks. All patients were fasted for a minimum period of 8 hours.

4.3.4 Upper Gastro intestinal endoscopy:

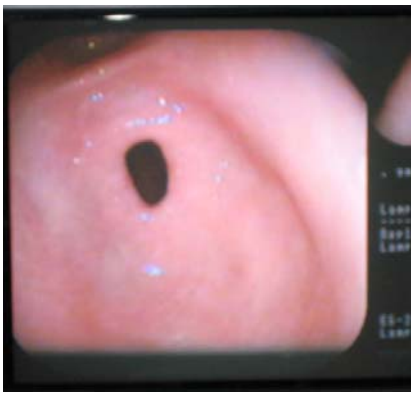
Prior to the procedure dentures and spectacles were removed. Pharynx was anaesthetized with 4 % xylocaine liquid. No sedation was given. Patients were put on left lateral position. Examination was made out by using flexible “PENTAX VEDIO ENDOSCOPY SYSTEM”

During this procedure the esophagus, stomach, duodenum were visualized for any mucosal abnormalities. After the procedure the instrument was washed in soap and water solution, kept in 2 % glutarldehyde solution for a minimum 4 minutes before reuse.

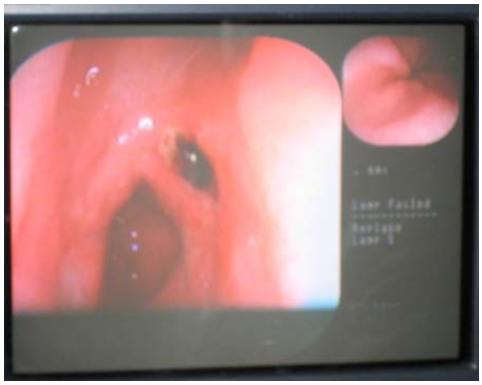
4.3.5) Limitation of Study :

1. H.Pylori infection is not excluded
2. No prior endoscopy examination done before starting aspirin

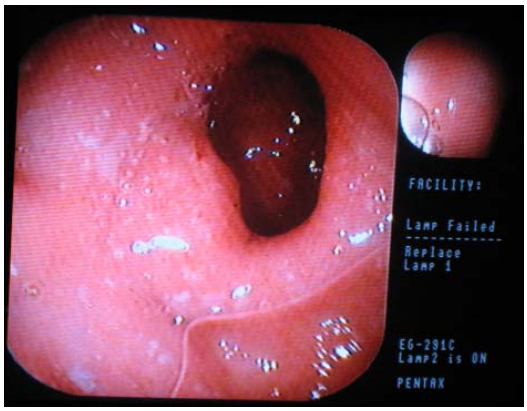
NORMAL ENDOSCOPY



GASTRIC ULCER



GASTRIC EROSIONS

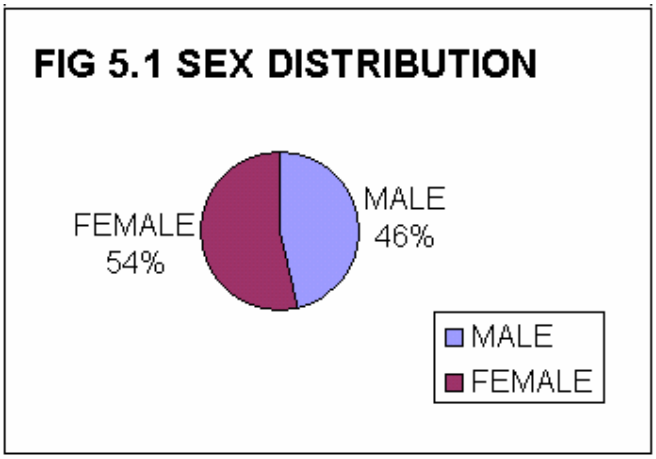


RESULTS AND OBSERVATION

5.1 SEX DISTRIBUTION

A total of 100 patients were studied. All of them were taking Aspirin for secondary prophylaxis for coronary artery heart disease. All Patients were on plain Aspirin, 150mg per day.

Among 100 patients 54 were females and 46 were males.

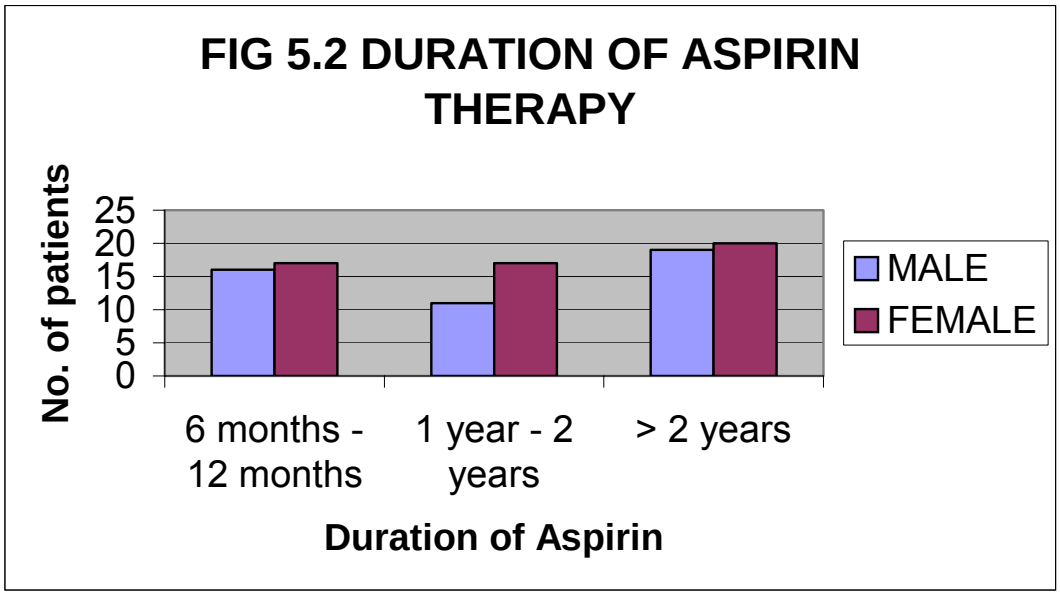


5.2 BREAKUP OF PATIENTS WITH REFERENCE TO DURATION OF ASPIRIN THERAPY.

TABLE 5.1 DURATION OF ASPIRIN

DURATION OF ASPIRIN	MALE	FEMALE	TOTAL
6 months - 12 months	16	17	33
1 year - 2 years	11	17	28
> 2 years	19	20	39
Total	**46**	**54**	**100**

The highest duration of Aspirin intake was 15 years and the lowest duration was 6 months.

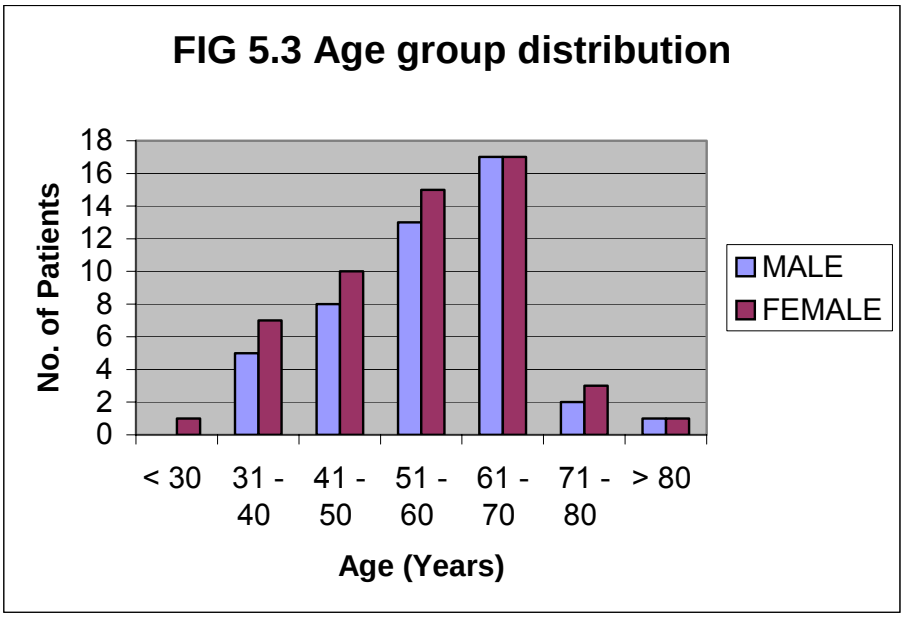


5.3 AGE WISE CLASSIFICATION OF PATIENTS:

TABLE 5.2 AGE GROUP DISTRIBUTION OF PATIENTS

AGE GROUP	MALE	FEMALE	TOTAL
≤ 30 YEARS	0	1	1
31 - 40 YEARS	5	7	12
41 - 50 YEARS	8	10	18
51 - 60 YEARS	13	15	28
61 - 70 YEARS	17	17	34
71 - 80 YEARS	2	3	5
> 80 YEARS	1	1	2
TOTAL	**46**	**54**	**100**

The highest age of patient participated in study was 85 years and lowest age of patient was 25 years. The majority of patients were 34(%) in 61-70 years age group.



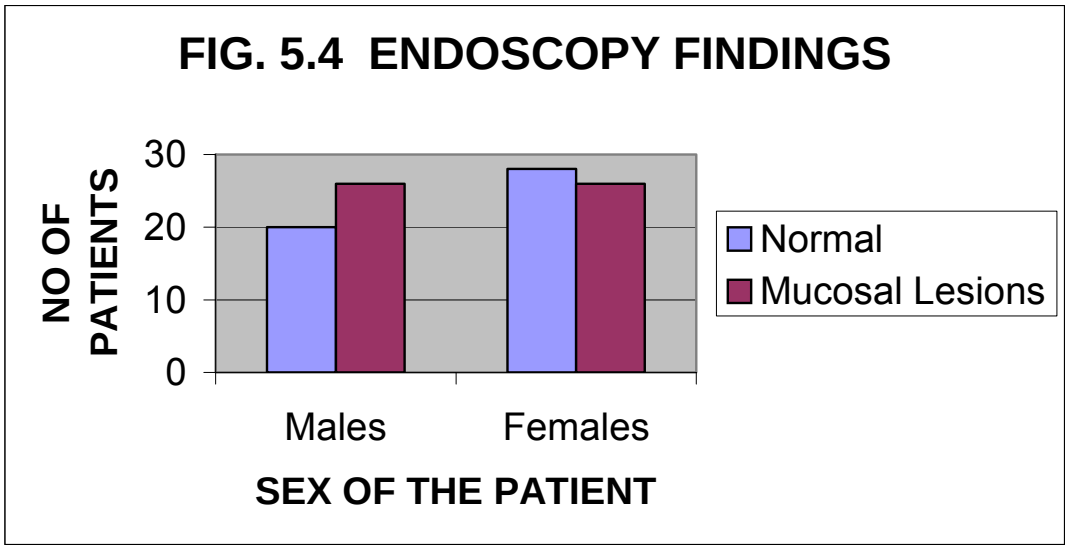
5.4 DISTRIBUTION OF MUCOSAL LESIONS AMONG MALES AND FEMALES:

Among 100 patients studied (52 %) patients had abnormal endoscopy.

Table 5.3 Distribution of Mucosal lesions among both sexes

Sex Group	UGI SCOPY		TOTAL
	Normal	Mucosal Lesions	
Males	20	26	46
Females	28	26	52
Total	**48**	**52**	**100**

In the current study 46 males were participated, among which 26 (56.5%) had mucosal lesions. In females 26 (40%) out of 54 had mucosal lesions.



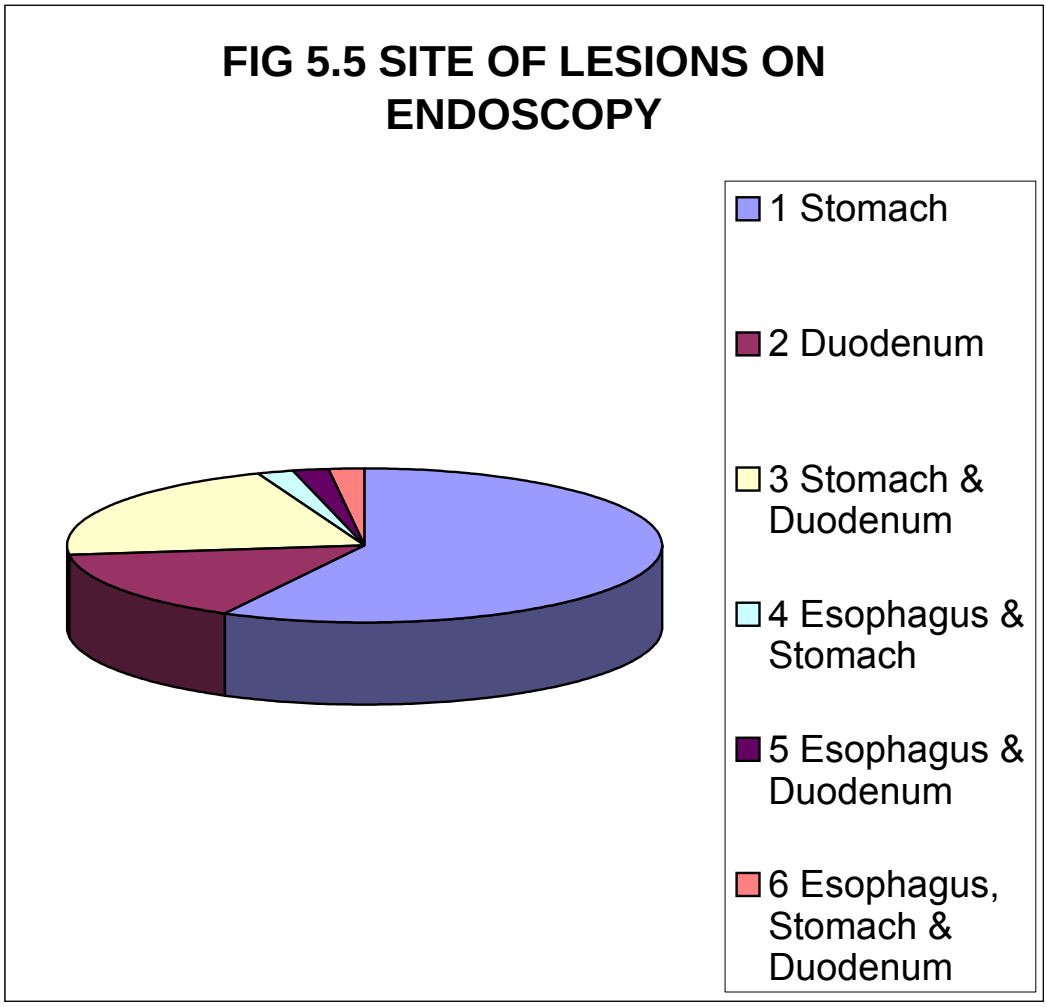
5.5 PREVALENCE OF SITE OF LESIONS ON ENDOSCOPY:

Among 100 patients 52 (%), patients had abnormal mucosal finding on upper GI endoscopy.

TABLE 5.4 SITE OF LESIONS ON ENDOSCOPY

S. NO	SITE OF LESIONS	NO. OF PATIENTS	PERCENTAGE
1.	Stomach	30	57.6%
2.	Duodenum	8	15%
3.	Stomach & Duodenum	11	21%
4.	Esophagus & Stomach	1	1.9%
5.	Esophagus & Duodenum	1	1.9%
6.	Esophagus, Stomach & Duodenum	1	1.9%

30(%) patients had abnormal findings in stomach alone. 8(%) patients had abnormal findings duodenum alone and 11(%) patients had abnormal findings in both stomach and duodenum.



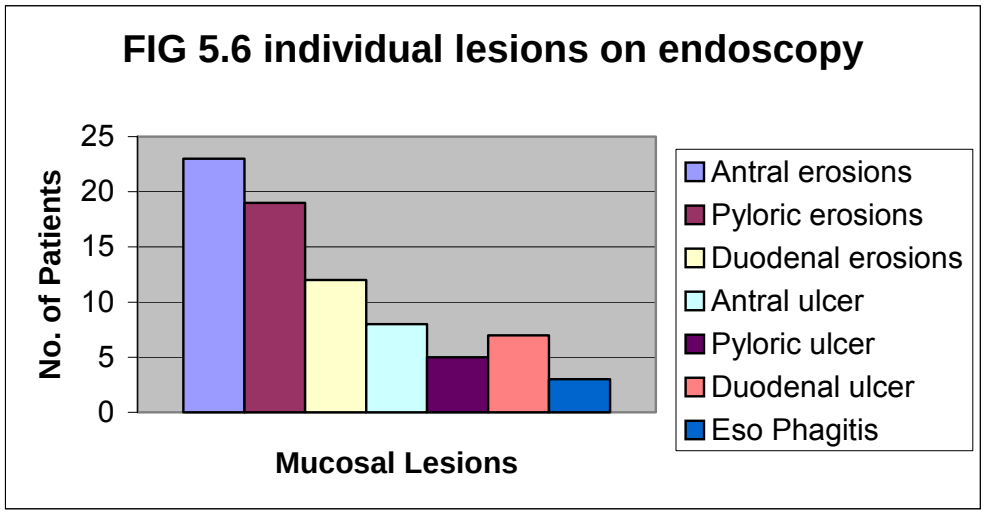
5.6 PREVALENCE OF NATURE OF INDIVIDUAL LESIONS ON ENDOSCOPY:

Among 100 patients, 25 patients (25%) had lesions at multiple sites. 27 had mucosal lesions and remaining 48 had normal UGI scopy findings.

TABLE 5.5 NATURE OF INDIVIDUAL LESIONS ON ENDOSCOPY

S.NO	LESIONS	NO. OF PATIENTS	PERCENTAGE
1.	Antral erosions	23	23%
2.	Pyloric erosions	19	19%
3.	Duodenal erosions	12	12%
4.	Antral ulcer	8	8%
5.	Pyloric ulcer	5	5%
6.	Duodenal ulcer	7	7%
7.	Esophagitis	3	3%

One patient had both antral and pyloric ulcer.



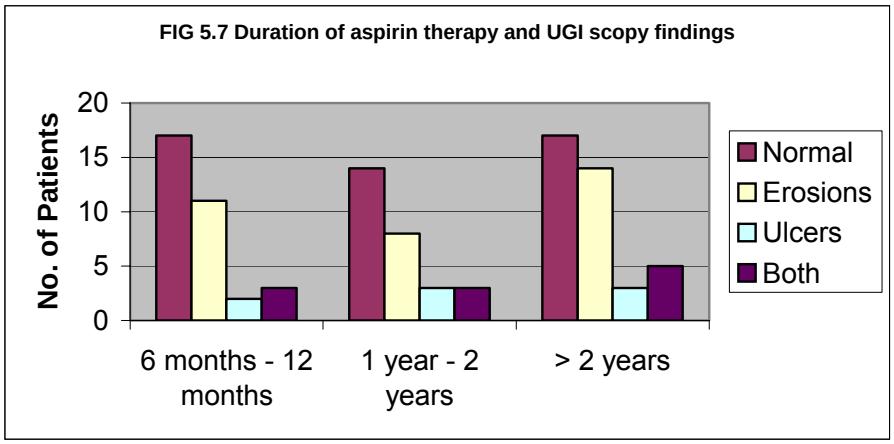
5.7 DURATION OF ASPIRIN THERAPY AND UGI SCOPY FINDINGS:

TABLE 5.6 DURATION OF ASPIRIN THERAPY AND UGI SCOPY FINDINGS

Duration of Aspirin	Total No- of Pts	UGI SCOPY			
		Normal	Erosions	Ulcers	Both
6 - 12 months	33	17	11	2	3
1 year - 2 years	28	14	8	3	3
> 2 years	39	17	14	3	5
Total	**100**	**48**	**33**	**8**	**11**

Among 100 patients studied, in 6 months - 1-year group, 17 (51.5 %) had normal endoscopy findings, 11 (33.5 %) had erosions, 2 (6 %) had ulcers and 3 (9 %) had both ulcer and erosions.

In the 1-2 year duration group, 14 (50 %) had normal endoscopy findings. 8 (28.5%) patients had erosions, 3 (10.7%) had ulcers and 3 (10.7 %) had both ulcer and erosions. In patients, more than 2 years duration group, 17 (43.5 %) had no mucosal abnormalities. 14 (35 %) had erosions, 3 (7.6 %) had ulcers and 5 (12.8 %) had both erosions, ulcers.



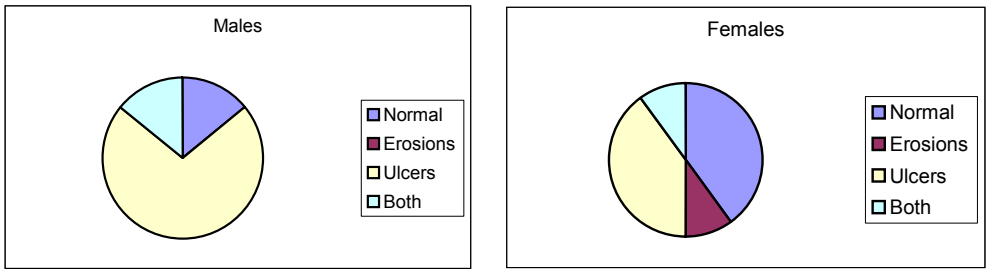
5.8 DYSPEPTIC SYMPTOMS AND UGI SCOPY FINDINGS:

Among 100 patients only seventeen (17 %) had various dyspeptic symptoms. Remaining 83 % had no symptoms referable to their upper gastro intestinal tract.

TABLE 5.7 DYSPEPTIC SYMPTOMS AND UGI SCOPY FINDINGS

Dyspeptic Symptoms	Total No. of Patients	UGI SCOPY			
		Normal	Erosions	Ulcers	Both
Males	7	1	0	5 (29.5%)	1 (5.8%)
Females	10	4	1 (5.8%)	4 (23.5%)	1 (5.8%)
Total	**17**	**5**	**1 (5.7%)**	**9 (53%)**	**2 (12%)**

FIG 5. 8 DYSPEPTIC SYMPTOMS AND UGI SCOPY FINDINGS



Of the 17symptomatic patients, 12(90.5 %) had mucosal abnormalities. Among which 9(53 %) had ulcers and 1 (5.8 %) had erosions, and 2 (12 %) had both. Of the 83 asymptomatic patients, 38 (46%) had mucosal abnormalities, 45 (54%) had normal findings.

5.9 NO OF RISK FACTORS & UGI SCOPY FINDINGS:

Four risk factors viz, smoking, alcoholism, history of prior peptic ulcer disease and other ulcerogenic drugs intake were studied. The following findings were noted.

TABLE 5.8 NO OF RISK FACTORS & UGI SCOPY FINDINGS

No. of Risk Factors	Total No. of Patients	UGI SCOPY		
		Normal	Ulcers	Erosions
0	48	32 (67%)	2 (4.7%)	14 (29%)
1	30	10 (33.35%)	10 (33.35%)	10 (33.35%)
2	18	5 (27.7%)	4 (22.2%)	9 (50%)
3	4	1 (25%)	3 (75%)	0
Total	**100**	**48**	**19**	**33**

Among zero risk factors, 67% (32) pts had normal findings. Whereas 3 risk factors, only 25 % (1) had normal findings. Among patients with no risk factors, 2 (4.7 %) had ulcers and 14 (29 %) had erosions.

Among patients with one risk factor, 10(33.3%) had ulcers and 10(33.3%) had erosions. Patients with two risk factors 4(22.2%) had ulcers and 9(50%) patients had erosions.

FIG. 5.9 NO OF RISK FACTORS AND UGI SCOPY FINDINGS

In this study 17 (%) patients had history of prior PUD out of 17 patients only 3 (17.6%) had normal findings and remaining 14 (82.35%) patients had mucosal lesions. Among mucosal lesions 6 (46%) had ulcers. Among patients with no history of PUD 38 (45%) had abnormal findings.

Out of 48 males, 28 (58%) had history of smoking. Among which 17 (61%) had mucosal lesions and ulcer in 6 (21.5%) patients.

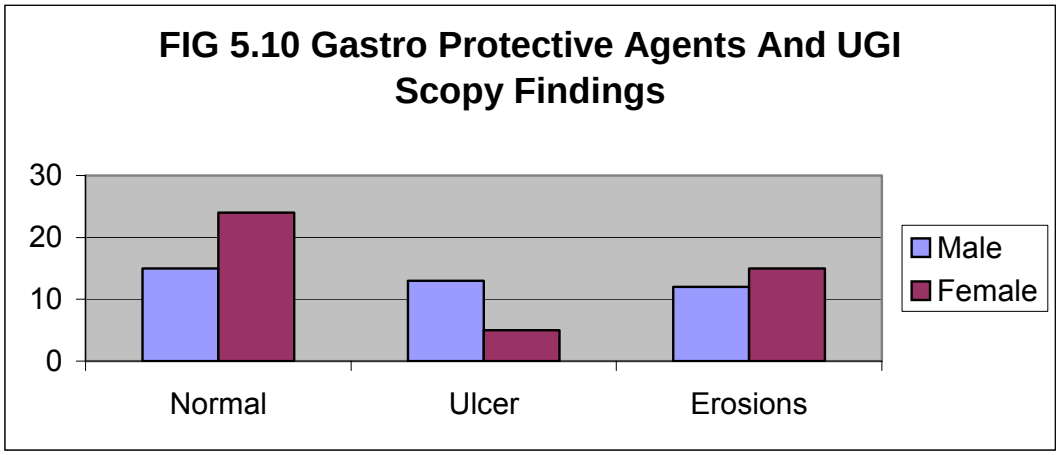
Among 48 patients participated in the study 21 (43.75 %) were alcoholics. Out of 21, 15 (71.5 %) had mucosal lesions and ulcer in 3 (14 %) patients.

5.10 GASTRO PROTECTIVE AGENTS AND UGI SCOPY FINDINGS:

Among 100 patients 84 were on gastro protective Agents. All are taking H2 receptors Antagonists. Among 84 patients 39 had (46.4%) normal findings. The remaining 27 (32%) had erosions and 18 (21 %) had ulcers.

TABLE 5.9 GASTRO PROTECTIVE AGENTS AND UGI SCOPY FINDINGS

H/O Gastro protective drugs	Total No. of Patients	UGI Scopy		
		Normal	Ulcer	Erosions
Male	40	15	13	12
Female	44	24	5	15
Total	**84**	**39 (46.4%)**	**18 (21 %)**	**27 (32 %)**



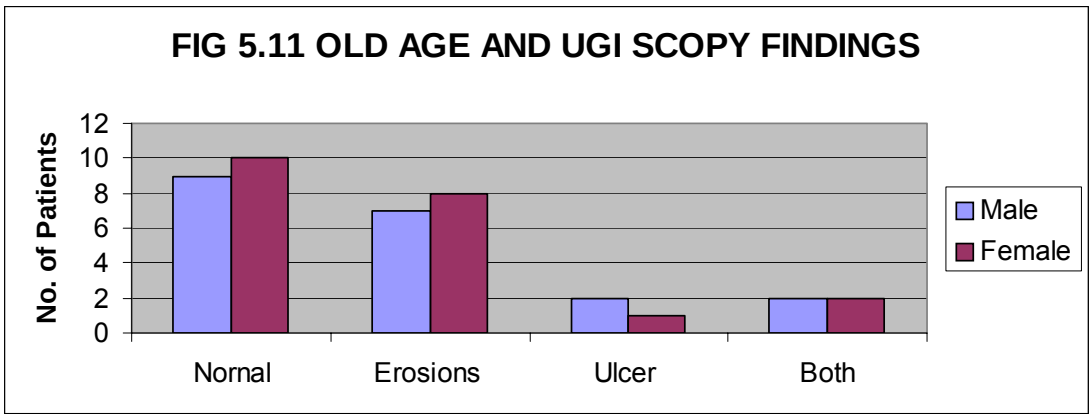
5.11 OLD AGE AND UGI SCOPY FINDINGS:

41 Patients were above age of 60 years. The UGI scopy findings were given below.

TABLE 5.10 OLD AGE AND UGI SCOPY FINDINGS

> 60 years	UGI Scopy findings				Total
	Normal	Erosions	Ulcer	Both	
Male	9	7	2	2	20
Female	10	8	1	2	21
Total	**19**	**15 (36.5 %)**	**3 (7 %)**	**4 (9.7%)**	**41**

Among 41 patients, 22 (53.6%) had abnormal findings in UGI Scopy. 15 (36.5%) patients had erosions, 3 (7%) had ulcers and 4 (9.7%) had both ulcers and erosions on UGI Scopy examination.



59 patients were below 60 years. Out of which 29 (49%) had abnormal endoscopy findings and 15 % had normal endoscopy.

5.12 HISTORY OF UGI BLEED & ENDOSCOPY FINDINGS:

Of 100 patients studied, 8 had history of upper Gastro intestinal bleed either melena or hematemesis.

TABLE 5.11 HISTORY OF UGI BLEED & ENDOSCOPY FINDINGS

H/O UGI Bleed	UGI Scopy				Total
	Normal	Erosions	Ulcer	Both	
Male	1	0	3	1	5
Female	1	0	1	1	3
Total	**2**	**0**	**4**	**2**	**8**

Among '8' patients 4 (50%) had ulcers, 25 % had both ulcers and erosions.

5.13 HISTORY OF OTHER ULCEROGENIC DRUGS:-

Of 100 patients studied, 12 had history of other ulcerogenic drugs like NSAIDs, corticosteroids of which 11(91.6%) had positive findings.

TABLE 5.12 HISTORY OF OTHER ULCEROGENIC DRUGS

H/O ulcerogenic drugs	Total	UGI Scopy		
		Normal	Ulcer	Erosions
Males	5	0	4	1
Females	7	1	3	3
Total	12	1	7 (58.3%)	4 (33.3%)

Among which 7 patients (58.3 %) had ulcers and 4 (33.3 %) had erosions.

Among remaining 88 patients most not taking other ulcerogenic drugs, only 12 (13.6%) had ulcers.

DISCUSSION

The gastro-duodenal toxicity of Aspirin is well known for many decades. Even a single dose of Aspirin can produce gastric erosion. Even though, the reduction of dose of Aspirin from 325 mg daily to 75 mg per day reduces the risk of upper gastro intestinal adverse effects, it does not totally eliminate the risk.

6.1) Gastro duodenal Mucosal defects by low dose Aspirin:-

Superficial Lesions:-

In the current study out of 100 patients 52 (%) of patients had Mucosal defects. Among which 42 % of patients had gastric erosions, 12 % had duodenal erosions, 3% had esophagitis.

Subepithelial petechiae or hemorrhages and erosions may be seen with acute and chronic Aspirin ingestion. Within 1 hour of single dose of Aspirin multiple subepithelial hemorrhages are seen in stomach. Repeated doses of Aspirin over a 24 hours period lead to gastric erosion, predominantly in the antrum[11].

In a study by Nema[39] *et al,* showed that, Mucosal defects were found in 48.4% users of low dose Aspirin.

In a study by Niv[40] *et al,* showed that, ulcers or erosions in 47.83 % of patients.

In various studies, found that gastric erosions are found at endoscopy in 30% to 50% of patients on low dose Aspirin therapy[11].

ULCERS:-

In the present study gastric ulcer was about 13 % and duodenal ulcer was 7 %. Antral Ulcer was common 8 %, of total 20 % of ulcers noted on endoscopy.

Cross sectional studies, in which endoscopy is performed in medical patients on chronic Aspirin therapy, the prevalence of gastric ulcers ranged from 9 to 31% and the prevalence of duodenal ulcers was 0 to 19%[11]. The crude prevalence rate of gastric ulcer in chronic Aspirin users is about 13 % and that of duodenal ulcer is about 11 %[41].

A study of chronic Aspirin intake of 61 patients with gastric ulcer revealed that 32 (52 %) take 15 or more tablets of Aspirin each week compared to 6 (10 %) age and sex matches control who took less amounts. The regular use of Aspirin was especially associated with ulcers in Antral region of stomach. (mayo clin. Proc.1975 oct: Cameron AJ)

6.2) Dyspeptic symptoms and endoscopy:

In the current study 17 % of patients taking Aspirin had severe dyspepsia, 55 % of patients with ulcerations were symptomatic and 45 % of patients with ulcerations were asymptomatic. 70.5 % of patients had mucosal abnormalities in the symptomatic group. Of the 83 symptomatic patients 46% had gastro duodenal mucosal abnormalities and 54 % had normal endoscopy findings.

Dyspeptic Symptoms are extremely common in patients taking Aspirin. In Aspirin myocardial infarction study, severe dyspepsia observed in 24 % of patients taking Aspirin and in 15 % patients given placebo[11].

Dyspepsia is more common in the first few weeks of therapy and tends to decline over time regardless of treatment. Patients wish NSAID-induced ulcer complication appears less likely to have symptoms than other ulcer patients. As many as 30 to 40 % of patients with significant mucosal ulcerations are asymptomatic[43].

6.3) Duration of Aspirin and UGI scopy findings:

If Aspirin is continued for several days Petechiae or hemorrhages seen with acute and chronic low dose Aspirin ingestion. In this study, patients who were on low dose Aspirin for less than a year, 51.5 % had normal UGI scopy findings, 33.5 % had erosions and 6 % had ulcers and 9 % had both ulcers and erosions. In the 1-2 year duration group, 50% had normal findings. 28.5% patients had erosions, 10.7% had ulcers and 10.7% both ulcer and erosions.

In those patients who were taking low dose Aspirin, more than 2 years, only 43.5 % had normal UGI scopy, 35 % had erosions, 7.6% had ulcers and 12.8% had erosions and ulcers.

In a study of Graham[18] *et al,* showed that if aspirin is continued for several days, the petechiae and erosions becoming less prominent. In a study by Soll[41] *et al,* showed that despite adaptation to low dose aspirin, gastric erosions are found at endoscopy in 30 to 50 % of patients on chornic NSAIDs. In various controlled prospective studies, conducted in those patients on long term NSAIDs patients, indicate that the risk of serious NSAIDs induced GI complications appear to be cumulative and linear[11].

This study revealed that as the duration of Aspirin therapy advances, the relative frequency of ulcers are increasing.

6.4) Distribution of mucosal lesions among both sexs:

In the current study 46 % of patients were males, among which 56.5 % had mucosal lesions. In females 40 %, out of 54 % of patients had mucosal lesions.

In a study by Gabriel[44] *et al,* found an equivalent risk between the sexs. The higher prevalence of mucosal lesions among males in the current study may be due to more risk factors.

6.5) Risk factors for aspirin induced GI lesions:

Certain group of aspirin taking patients appear to be greater risk for development of aspirin induced ulcer complications.

In this study 48 % patients had no risk factors and among which 67 % of patients had normal UGI scopy findings. Among patients with one risk factor 33.3 % had normal UGI scopy. Among patients with two risk factors 27.7 % had normal UGI scopy and patients with 3 risk factors, only 25 % had normal scopy findings.

Studies by Wolfe[11] *et al,* Laine[45] *et al,* Hoachain[46] *et al,* showed that multiple factors including increasing age, history of ulcer or GI complications, concomitant anticoagulation therapy, concomitant corticosteroid use and high dose NSAIDs use. It also revealed that, patients with more numbers of risk factor had more gastric mucosal lesions especially ulcers.

6.6) Alcoholism and Ulcers:

In the current study, 48 males were participated, among which 43.75 % were alcoholics. Out of which 71.5 % had mucosal lesions and 14 % had ulcers.

In a study by Kaufman[47] *et al,* revealed that among current drinkers aspirin taken at least every other day 325mg / day is associated with a seven

fold increased risk of upper GI events when compared with those who do not drink.

6.7) History of prior peptic ulcer disease and UGI scopy findings:

In this study 17% of patients had history of prior PUD. Out of which 82.35 % had mucosal lesions and 17.65 % had normal UGI scopy findings. Among patients with no history of prior PUD 45 % abnormal mucosal lesions.

In various studies, concluded that the most important risk factor for aspirin induced GI complications is history of prior PUD, which increase the risk of Aspirin induced GI events by two fold to four fold[16].

6.8) Old age and UGI socpy findings:

In the present study, 41 % of patients were above age of 60 years. Among which 53.6% had abnormal findings in UGI scopy. 36.5 % had erosions and 7 % had ulcers, 9.7 % had both ulcers and erosions. In less than 60 years age group patients, only 49 % had abnormal findings.

In a study by Gabriel[44] *et al,* showed that the relative risk is greater than 5 in aspirin users older than 60 years age but less than 2 in younger patients. 8 Randomized , placebo controlled studies by Sibilia[48] *et al,* showed that erosions, particularly gastric erosions are more frequent in elderly than younger patients.

In the prospective aspirin myocardial infarction study, there was linear relation in the aspirin-treated group between ulcer complications and the age of patients[11]. In a study by Lanza[49] *et al,* showed that the likely hood of serious events appears to increase in liner fashion, with no significant

increase in ulcer bleeding reported among patients aged 35 – 49 years and 2-9 fold increase in patients aged 50 to 64 years.

6.9) History of other ulcerogenic drugs and UGI scopy findings :

Of 100 patients studied, 12 % had history of other ulcerogenic drugs like NSAIDs, conticosteroids. Of which 91.6% had positive findings and 58.3% had ulcers.

Among patients with no history of other ulcerogenic drugs, 13.6% had ulcers.

In various studies (by silverstein *et al,* Stornch *et al,* Laine *et al,)*[11 & 16] revealed that low dose aspirin with concurrent NSAIDs, markedly increases the risk of Aspirin induced ulcers by two fold to six fold above the risks associated with aspirin alone.

6.10) History of UGI bleed and endoscopy findings:

In the current study 8 % of patients had history of UGI bleed. Among which 50% had ulcers, 25 % had both ulcers and erosions.

In a study by Lans[50] *et al,* showed that peptic ulcers accounted for 42 % of UGI bleed, in patients on Aspirin. In a meta analysis of 24 randomised controlled trials by Sheena[51] *et al,* showed that at doses below 163 mg/day, GI bleed occurred in 2-3% of patients taking Aspirin.

In a review by Sibilia[48] *et al,* showed that a non-significant increase in esophageal, gastric and duodenal ulcers during treatment with low dose aspirin, but a significant increase in bleeding ulcers.

6.11) Gastro protective agents and UGI scopy findings:

In the current study, 8.4 % of patients were on gastro protective agents. All are taking H2- receptor antagonists. Among them, 46.4% had normal findings, 32% had erosions and 21 % had ulcers.

When aspirin is continued, ulcer healing appear to be delayed and is largely dependent on the initial ulcer diameter.

In a randomised study by Lana Caster- Smith MS[52] *et al,* 190 patients with endosopically confirmed gastro duodenal ulcers, patients were assigned to continue, or discontinue Aspirin therapy. All patients were treated with Ranitidine 150 mg BD. After 8 weeks, healing of gastric ulcers was observed in only 63% of those on drugs, compared with 95 % of those who stopped them.

For duodenal ulcers, the corresponding 8 week healing rates were 84 % in the group continuing Aspirin and 100 % in those who discontinued them.

It appears that although healing of large gastric ulcers is delayed when Aspirin use is continued, healing may be achieved provided H2 RA therapy is continued for an extended period of time. However with advent of more potent anti- secretory agents such as PPIS, the use of H2RA in the healing of Aspirin-related ulcers is no longer recommended as first line therapy[38].

CONCLUSION

1) This study on endoscopic findings in low dose aspirin therapy shows, 52 % of patients had abnormal mucosal findings, whereas 48% of patients had normal study. So the incidence of abnormal endoscopic findings is almost the same as normal endoscopy findings.

2) Various Upper GI lesions noted in this study as follows:-

    Antral erosions 25 %

    Pyloric erosions 19 %

    Duodenal erosions 12 %

    Antral ulcer 8 %

    Pyloric ulcer 5 %

    Duodenal ulcer 7 %

    Esophagitis 3 %

Antral erosions is the commonest abnormality noted in this study. Antral ulcer is commonest among ulcers. Prevalence of mucosal lesion is lowest in esophagus (3 %).

3) The mucosal lesions induced by low dose aspirin is more in stomach rather than duodenum.

4) H2 receptor is not a safe drug to prevent the upper GI lesions during low dose aspirin therapy.

5) 70.5 % of Dyspeptic patients had abnormal findings in gastro duodenal mucosa. This shows dyspeptic symptoms correlate well with endoscopic findings.

6) If the duration of low dose aspirin consumption increases, likelihood of having ulcers is more.

7) If the patient has more risk factors, more chances of having mucosal lesions.

8) Old age is associated with more mucosal lesions.

BIBLIOGRAPHY

1. Anne burke., Emer Smyth., and Garret A.Fitz Gerald. **Good-man and Gillmans's the Pharmacological bais of therapeutics**, 11th ed. New York: M C Graw-Hill, 2006 : 673.

2. Seibert.K., Zhang.V., Lehay.K., *et al.* Distribution of cox-1 and cox-2 in normal and inflamed tissues. **Adv.Exp.Med.Biol., 1997,** 400A:167-170.

3. Breder. C.D., Dewitt.D., and Kraig,R.P. Characterization of inducible cycloxygenase in rat brain. **J.Comp Neurol., 1995,** 355: 296-315.

4. Topper, J.N., Caij., Falb.D., and Gimbrone., Identification of vascular endothelial genes differentially responsive to fluid mechanical stimuli: Cyclo genxge-2, manganese superoxide dismutase, and endothelial cell nitric oxide synthase are selectively up regulated by steady laminar shear stress. P**roc.Natl.Acad. Sci.USA, 1996**, 93: 1047-1422.

5. Serhan, C.N., and Oliw, E. Un orthodox routes to prostanoid formation: new twists in cyclooxygenase-initiated pathways. **J.Clin.Invest., 2001**, 107: 1481-1489.

6. Sean C sweetman. **The complete drug reference-martindale**, 34th-ed. London: Pharmaceutical press, 2005:18.

7. Pederson, A.K., and FitzGerald, G.A. Dose related kinetics of Aspirin: pre systemic Acetylation of platelet cyclooxygenase **N.Engl.Jmed., 1981,** 311: 1206-1211.

8. Richard A.Harvey., Pamela C., champe. **Lippincott's illustrated reviews-pharmacolog**, 3rd ed. Wolters : India, 2007: 500.

9. Gerald K.Mcevoy. **AFHS-Drug information essentials, 2005-2006**; Bethesda, 2005: 146

10. Laurnce L.Brunton., Jhon S.lazo., Keith L.Parker. **Good man and Gilman's The pharmacological basis of Therapeutics**, 11th ed. New York: Mc Graw-Hill, 2006:683.

11. TADATKAYAMADA.. **Text book of Gastroenterology**, 3rd ed. Philadelphia: lippincott Williams and Wilkins, 1999. : 1326-27, 1373-91.

12. Fauci., Braunwald., Kasper., Longo., Jameson., Loscalzo., **Harrison's principles of internal medicine, 17th ed.** New York: Mc Graw-Hill, 2008: 1855-67.

13. Allen A, Hutton.D., MCqueen S, Garner A. Dimensions of gastro duodenal surface pH gradients exceed those of adherent mucus gel layers. **Gastro enterology 1983**; 85:463.

14. Flemstron G, Garner A. Gastro duodenal HCO_3 transport characteristics and proposed role in acidity regulation and mucosal protection. **Am.J. physiol 1982**; 242: G183.

15. Feil W, Klimesch , Karner P *et al.* Importance of alkaline micro environment for rapid restitution of the rabbit duodenal mucosa in vitro. **Gastroenterology 1989**; 97:112.

16. Marf Feldman, Lawren S: Friedman, Lawrence J. Brandt. **Sleisenger and Fordtran's gastro intestinal and liver diseases 8th ed.** Saunder: Philadelpia 2006: 1092-1096, 1117.

17. Gregory G.Gins berg., Michael L.Kochman. **The requisites in gastro enterology-Endoscopy and gastro intestinal radiology**, Mosby : Philadelphia, 2004: 1-6.

18. Graham Dy, SmithJL. Aspirin and the stomach. **Ann. intermed 1986**; 104: 3908.

19. Derry S,Loke YK. Risk of gastro intestinal haemorrage with long term use of Aspirin: meta-analysis. **BMJ 2000**: 1183-7.

20. Brooks PM, Day RO. Nonsteroidal anti inflammatory drugs-differences and similarities. **N.Engl.J.Med 1991**; 324:1716.

21. Somasundaram G, Sigthorsson RJ, Simpson J, *et al.* Uncoupling of intestinal mitochondrial oxidative phosphorylation and inhibition of cyclooxygenase are required for the development of NSAID-Gastroenteropathy in rat. **Aliment.Pharmacol. Thera**.14:639, 2001.

22. Darling RL, Romero JJ, Dial EJ, *et al.* ; The effects of Aspirin on gastric mucosal integrity, surface hydrophobicity, and prostaglandin metabolism in cyclooxygenase knock out mouse. **Gastroenterology 127**; 94, 2004.

23. Yeoman.N,D, *et al.* ; Approches to healing and protection of NSAID induced ulcers. **A.J. medi 2001**; 114: 257-263.

24. Dhikav. *et al.* Aspirin misconceptions. Drugs news and views; 2001: 64-65.

25. Griffin.M.R.,Piper; J.M; Daugherty, J.R., Snowden.M, and Ray WA. nonsteroidal anti-inflammatory drug use and increased risk of peptic ulcer disease in elderly person. **Ann-int-med.1991**; 114: 257-263.

26. Andrade, SE., Gurwitz., J.H, and Fish.L.S. The effect on an treatment to over counter switch on medication prescribing patterns and utilizations of physician services: the case of H2- receptor antagonists. **Medical care 1999**; 37:: 424-430.

27. SING.G, *et al.* Recent considerations in non steroidal anti-inflammatory drug gastropathy. **AM.J.medicine: 1999**; 105; 31s-38s.

28. Rogind; H *et al.* Comparison of etodolac and piroxicam in patients with OA of hip/knee. A prospective, randomized, double-blind, controlled multi centre study. **Clinical drug investigations: 1997**; 13; 66-78.

29. Hooper L, Brown T., Elliott. RJ Payane.K., Roberts., C and symmons.D. The effectivness of five strategies for the prevention of gastro intestinal toxicity induced by non-steroidal anti-inflammatory drugs. Systematic review. **BMJ 2004**; 329: 948-952.

30. Lucker., P.W; Pawlowski., Friedrchi.I, Faiella.F, magni,E. Double blind, randomized multi centre clinical study evaluating the efficacy and tolerability of Nimesulide in comparison with etodalac. **European.J of and Rheu. 1994**; 14: 29-38.

31. Paulsen.G.A., Baigun. S., Defigveiredo.J., and Gomes.DF. Efficay and tolerability comparison of etodolac and piroxicam in the treatment of patients with OA knee. **Current medical research & opinion ; 1991**: 12; 401-412.

32. Peura.D.A. *et al,* prevention of NSAIDs associated gastro intestinal symptoms and ulcer complications. **AJ.Med 2004**: 177; 639- 715.

33. Dalton. S.O., Jhohansen.C., Mellem kjaer. Use of selective serotonin reuptake inhibitors and risk of UGI bleeding. **Arch.of Int.Med. 2003**:163; 59-63.

34. Vikas.D., Sindhu.S., Swati. A.C., Kul jeet.S., Anand. Non steroidal drug induced GI toxicity. **Journal of investigational allergology and clinical immunology; 2003**; 4; 315-22.

35. Bijlsma JW. Treatment of NSAID-Induced gastro intestinal lesions with cimetidine: an international multi centre collaborative study. **Aliment pharmacol. Ther.1988**; 2 Suppl:85-95.

36. Van Groendael.JH, markusse HM., Dijkmans BA *et al.* The effect of ranitidine on NSAID related dyspeptic symptoms with and without peptic ulcer disease of patients with rheumatoid arthritis and osteoarthritis. **Cli. Rheumatol.1996**; 15 (5): 450-56.

37. Ekstrom.P, Carling L, Wetterhus S, *et al*. Prevention of peptic ulcer and dyspeptic symptoms with omeprazole in patients receiving continuous NSAIDs. **A Nordic multi centre study. Scand J.Gastro enterol**.

38. Michael Wolfe M., **Therapy of digestive disorders 2nd ed**. Elsevier: Philadeldhia; 2006: 295-297.

39. Nema.H. *et al*. Investigation of gastric and duodenal mucosal defects caused by low dose aspirin in patients with ischaemic heart disease. **J. Clin, Gastroenterol. 2008**.Sep-5.

40. Niv.Y., Battler A., Abuksis G., Gal.E., Endoscopy in asymptomatic minidose aspirin consumers. **Dig. Dis.Sci.2005 jan**; 50 (1) : 78-80.

41. Soll AH, Weinstein WM, Kurata.J, Mccarthy D. Non steroidal anti-inflammatory drugs and peptic ulcer disease. **Ann.intern med. 1991**; 114: 307.

42. MC Carthy D. M. Non steroidal anti inflammatory drug – induced ulcers: management by traditional therapies. **Gastro enterology 1989**; 96:662.

43. MC Carthy D. Non steroidal anti-inflammatory drug- the clinical dilemmas. **Scand J. Gastroenterol. 1992**; 27:9.

44. Gabriel Se, Jakkimaineen L, Bombardier C. Risk for serious gastro intestinal complications related to use of Non-steroidal anti-inflammatory drugs. A meta analysis. **Ann. Intern med. 1991**: 115 (10):787-796.

45. Laine.L *et al*. Gastro intestinal bleeding with low dose Aspirin. **Aliment .Pharmacol. Ther. 2006 sep 15;** 24 (6) : 897-908.

46. Hochain.P., Capet C, Colin R. Digestive complications of Aspirin. **Rev.med.Interne. 2000 mar**; 21 supp1: 505-595.

47. Kauf Man DD, Kelly JP, Wiholm BE, *et al*. The risk of acute major upper gastro intestinal bleeding among users of Aspirin and ibuprofen at various levels of alcohol consumption. **A.M.J. Gastroentero l994**: 3189-1999.

48. Sibilia J, Ravaud P, MarckG, *et al*. Digestive and hemorrhage complications of low dose aspirin. P**resse Med . 2003 Nov 22**; 32: 17-28.

49. Lanza LL, Walker AM, Bornichak EA *et al*. Peptic ulcer and gastro intestinal hemorrhage associated with non steroidal anti-inflammatory drugs use in patients younger than 65 years. **Arch.inter.med 1995**; 155 (13): 1371-1377.

50. Lans A, Sekr MC, Hirgchowitz BI. Objective evidence of Aspirin use in both ulcer and non ulcer and lower gastro intestinal bleeding. **Gastroenterology 1992**; 103:862.

51. Sheena Derry, Yoon Kong Loke, Risk of gastrointestinal halmorrhage of aspirin: **Meta analysis. BMJ 2000**; 321: 1183-1187.

52. Lancaster-Smith MJ, Jader berg ME, Jackson DA.Ranitidine in the treatment of Non steroidal anti-inflammatory drug associated gastric and duodenal ulcers. **GUT 1991**: 32(3): 252-25

PROFORMA

UPPER GI ENDOSCOPY FINDINGS IN LOW DOSE ASPIRIN CONSUMERS:

Patient's Name :

Age / Sex :

O.P/I.P No. :

Diagnosis :

Dose of Aspirin :

Duration of Aspirin :

H/O prior PUD :

H/O smoking :

H/O Alcoholism :

H/O other ulcerogenic drugs :

H/O Dyspepsia :

H/O Upper Abdominal Pain :

H/O Gastro protective drugs :

H/O UGI Bleed :

Examination:

Anemia :

Pulse :

BP :

Abdomen :

Cardiovascular system :

Respiratory system :

Nervous system :

UGI Scopy findings:

Date :

Esophagus :

Stomach :

Duodenum :

UPPER G I ENDOSCOPY FINDINGS IN LOW DOSE ASPIRIN CONSUMERS:

MASTER CHART

S. No.	Patient's Name	Age & Sex	O.P / I.P No.	Duration of the Aspirin	RISK FACTORS				H/O Gastro Protective Drugs	H/O Dyspeptic Symptoms	H/O UGI Bleed	UGI SCOPY	
					H/O Prior PUD	H/O Smoking	H/O Alcoholism	H/O Other Ulcerogenic drugs				Esophagus	Stomach
1	PALANIYANDI	45 / M	995175	5 YEARS	-	+	+	-	H2A		+	N	N
2	SARASWATHI	65 / F	1002890	2 YEARS	-	-	-	-	-	-	-	N	ANTRAL EROSIONS
3	MUNIAMMAL	61 / F	2201/07	7 YEARS	-	-	-	-	-	-	-	N	ANTRAL EROSIONS
4	RAJARAJAN	61 / M	1004508	15 YEARS	-	-	-	-	-	-	-	N	PYLORIC EROSIONS
5	RANI	37 / F	1004724	6 MONTHS	-	-	-	-	-	-	-	N	N
6	RAJAM	50 / F	1004683	6 MONTHS	-	-	-	-	-	+	-	N	N
7	UDHYA SURIYAN	45 / M	3531/08	6 MONTHS	-	+	+	+	H2A	+	-	N	ANTRAL ULCER & EROSIONS
8	LAKSHMI	60 / F	4362/03	5 YEARS	-	-	-	-	H2A	-	-	N	N
9	LATHA	38 / F	992170	8 MONTHS	+	-	-	-	H2A	+	-	ESOPHAGITIS	ANTRAL EROSIONS
10	KALIYAMMAL	65 / F	1003259	8 MONTHS	+	-	-	-	H2A	-	+	N	ANTRAL ULCER
11	GRACEMARY	55 / F	1004035	10 YEARS	-	-	-	-	H2A	-	-	N	N
12	SURESH	30 / M	1003191	7 MONTHS	-	+	+	-	H2A	+	-	N	N
13	THANGARAJ	50 / M	1003861	5 YEARS	-	+	-	+	H2A	-	-	N	N
14	SIRONMARY	45 / F	3918/08	9 MONTHS	+	-	-	-	H2A	-	-	N	N
15	SARATHAMBAL	94 / F	1003708	3 YEARS	-	-	-	-	H2A	-	-	N	N
16	CHKKARAVARTHY	62 / M	1004166	3 YEARS	+	+	-	+	H2A	+	+	N	ANTRAL & PYLORIC EROSIONS
17	KARUPAIYAN	50 / M	1004155	1.6 YEARS	-	+	+	-	H2A	-	-	N	PYLORIC EROSIONS
18	SUNDARAMBAL	40 / F	1005579	10 YEARS	-	-	-	-	H2A	-	-	N	N
19	JEGADAMBAL	65 / F	1005393	12 YEARS	-	-	-	-	H2A	-	-	N	PYLORIC & ANTRAL EROSINS
20	SUNDARAVALLI	60 / F	1005609	1.8 YEARS	-	-	-	-	H2A	-	-	N	N
21	PUSPHAM	38 / F	1005050	1.6 YEARS	-	-	-	-	H2A	-	-	N	N
22	THIYAGARAJ	78 / M	1005531	5 YEARS	-	-	+	-	H2A	-	-	N	N
23	RANGABHASYAM	62 / M	1005228	4 YEARS	-	-	-	-	H2A	+	+	N	N
24	NAGARAJAN	70 / M	100564	2 YEARS	-	+	-	-	H2A	-	-	N	N
25	GOVINDHARAJ	50 / M	1005991	5 YEARS	-	-	+	+	H2A	-	-	N	ANTRAL EROSIONS
26	UMARANI	53 / F	1006212	6 MONTHS	-	-	-	-	H2A	-	-	N	N
27	LAKSHMI	25 / F	1006148	6 YEARS	-	-	-	-	H2A	-	-	N	N
28	MANORANJTHAM	65 / F	1008306	5 YEARS	-	-	-	-	H2A	-	-	N	N

29	MUTHAIYAN	70 / M	1008058	5 YEARS	-	+	+	-	H2A	-	+	N	N
30	SWAMINATHAN	65 / M	1008346	6 MONTHS	+	+	+	-	H2A	+	-	N	ANTRALEROSIONS & ULCER
31	MANORANJITHAM	78 / F	1008441	2 YEARS	-	-	-	+	H2A	-	-	N	PYLORIC EROSIONS & ANTRAL ULCER
32	BALASAMY	60 / M	1003690	1.2 YEARS	-	+	-	-	H2A	-	-	N	N
33	LALITHA	50 / F	1004074	1.6 YEARS	-	-	-	-	H2A	-	-	N	PYLORIC EROSIONS
34	PATTU	65 / F	1004341	3 YEARS	-	-	-	-	H2A	+	-	N	N
35	GOVINDHARAJ	60 / M	1004847	8 MONTHS	-	+	+	-	H2A	-	-	N	N
36	GLIAMARY	43 / F	1003650	1.3 YEARS	+	-	-	-	H2A	-	-	N	ANTRAL EROSIONS
37	RAMU	58 / M	1009075	5 YEARS	-	-	+	-	H2A	-	-	N	PYLORIC EROSIONS
38	SAROJA	66 / F	1009127	6 YEARS	-	-	-	-	-	-	-	N	N
39	MUNIAMMAL	42 / F	5923/07	1.6 YEARS	-	-	-	+	H2A	+	-	N	PYLORIC ULCER
40	KRISHNAMMAL	85 / F	989742	10 YEARS	-	-	-	-	H2A	-	-	ESOPHAGITIS	N
41	VEERAMMAL	65 / F	991265	1.6 YEARS	-	-	-	-	-	-	-	N	ANTRAL EROSIONS
42	MAHALINGAM	85 / M	1009737	3 YEARS	-	-	-	-	H2A	-	-	N	N
43	RAJAGOPAL	65 / M	1009841	6 MONTHS	-	+	+	-	H2A	-	-	N	ANTRAL EROSIONS
44	NAVAMANIAMMAL	70 / F	991431	1.2 YEARS	-	-	-	-	H2A	-	-	N	N
45	VIAMALA	50 / F	993175	2 YEARS	+	-	-	-	H2A	-	-	N	ANTRAL & PYLORIC EROSIONS
46	KALIYASUNDARAM	70 / M	991805	7 MONTHS	-	+	-	-	H2A	-	-	N	N
47	DHABILAK BEGUM	35 / F	992296	8 MONTHS	-	-	-	+	H2A	-	-	N	N
48	MARUTHAMBAL	60 / F	993519	1 YEAR	-	-	-	-	H2A	-	-	N	ANTRAL EROSIONS
49	ANANTHAKUMAR	45 / M	1009817	3 YEARS	-	+	+	-	H2A	-	-	N	N
50	RAJENDRAN	63 / M	1010197	2 YEARS	-	+	-	-	H2A	-	-	N	ANTRAL EROSIONS & PYLORIC ULCER
51	PATTU	70 / F	994269	2.6 YEARS	+	-	-	-	H2A	-	+	N	N
52	RAJAMMAL	65 / F	994183	6 MONTHS	-	-	-	-	H2A	-	-	N	N
53	VIJIYALAKSHMI	55 / F	999557	8 MONTHS	-	-	-	+	H2A	-	-	N	PYLORIC & ANTRAL EROSINS
54	JOTHIAMMAL	50 / F	996068	1.2 YEARS	-	-	-	-	-	-	-	N	N
55	SRINIVASAN	69 / M	1009767	3 YEARS	-	+	+	-	H2A	-	-	N	N
56	MARAGATHAM	46 / F	996929	2 YEARS	-	-	-	-	H2A	-	-	N	N
57	DHINAKARAN	39 / M	1009780	6 MONTHS	+	+	-	-	H2A	-	-	N	PYLORIC ULCER & EROSIONS
58	SUSHILA	45 / F	1002876	6 MONTHS	-	-	-	-	H2A	-	-	N	ANTRAL ULCER
59	ANJAMMAL	60 / F	992975	2 YEARS	+	-	-	-	H2A	-	-	N	PYLORIC EROSIONS
60	DHANABAKKIAM	58 / F	993871	8 YEARS	-	-	-	-	H2A	-	-	N	N
61	VADUGAMBAL	52 / F	993901	1.10 YEARS	-	-	-	-	H2A	+	-	N	N
62	ANJAMMAL	55 / F	995699	3 YEARS	-	-	-	-	H2A	+	-	N	N
63	AYYASAMY	67 / M	1009731	8 MONTHS	-	+	+	-	-	-	-	N	N
64	RAMU	60 / M	1009800	6 MONTHS	-	+	-	-	H2A	-	-	N	N
65	JEYALAKSHMI	80 / F	996132	5 YEARS	-	-	+	-	H2A	-	-	N	PYLORIC EROSIONS
66	CHANDRA	50 / F	996816	8 MONTHS	-	-	-	+	H2A	-	-	N	ANTRAL EROSIONS
67	ANJALAI	60 / F	998290	1.4 YEARS	-	-	-	-	H2A	-	-	N	N
68	VASANTHA	40 / F	998492	9 MONTHS	+	-	-	-	H2A	-	-	N	PYLORIC EROIONS

69	DURAIRAJ	70 / M	1009481	10 YEARS	-	+	-	-	H2A	-	-	N	ANTRAL EROSIONS & ULCER
70	GOVINDHARAJ	70 / M	1008334	2 YEARS	+	+	-	-	H2A	-	-	ESOPHAGITIS	ANTRAL EROSIONS
71	PANCHAVARNAM	60 / F	999180	2.6 YEARS	-	-	-	-	-	-	-	N	N
72	SARATHAMBAL	70 / F	999175	3 YEARS	-	-	-	-	H2A	-	-	N	PYLORIC EROSIONS
73	SIVAGAMI	65 / F	1001080	6 MONTHS	-	-	-	-	H2A	-	-	N	N
74	SWAMINATHAN	51 / M	7530/07	1.3 YEARS	+	-	-	-	H2A	-	-	N	N
75	MANICKKAM	54 / M	3484	6 MONTHS	-	+	+	-	H2A	+	-	N	PYLORIC EROSIONS
76	PUSPHAM	70 / F	1002306	3 YEARS	+	-	-	-	H2A	+	-	N	PYLORIC ULCER & EROSIONS
77	PAPATHI	65 / F	1003126	8 MONTHS	-	-	-	+	H2A	-	-	N	N
78	MARIAMMAL	70 / F	1005958	5 YEARS	-	-	-	-	H2A	-	-	N	N
79	AJIJA BEEVI	70 / F	5689/08	1.3 YEARS	-	-	-	-	H2A	-	-	N	N
80	SARAVANAN	38 / M	1010804	2.3 YEARS	+	+	-	-	H2A	-	-	N	ANTRAL EROSIONS
81	PALANIVEL	60 / M	1010878	8 MONTHS	-	-	-	-	H2A	-	-	N	N
82	SAGAYAMARY	51 / F	1011792	6 MONTHS	-	-	-	-	H2A	-	-	N	N
83	MURUGAIYAN	75 / M	9648107	1.6 YEARS	-	-	+	-	-	-	-	N	N
84	ANBU	40 / M	1011312	8 MONTHS	-	+	+	-	H2A	-	-	N	N
85	AKBAR HUSSAIN	61 / M	1010392	11 MONTHS	-	-	-	-	-	-	-	N	N
86	BHADMAVATHI	40 / F	4766108	6 MONTHS	-	-	-	-	H2A	+	-	N	ANTRAL EROSIONS
87	CHANDRA	57 / F	1644/06	2.6 YEARS	-	-	-	-	-	+	+	N	ANTRAL ULCER & EROSIONS
88	JULEKHAKHAN	56 / F	8433107	1.2 YEARS	-	-	-	+	H2A	+	-	N	N
89	KANNAN	60 / M	789/06	2.6 YEARS	+	-	-	-	H2A	-	-	N	PYLORIC EROSIONS
90	THANGAIYAN	54 / M	990495	1.6 YEARS	-	+	+	-	H2A	-	-	N	N
91	RAJU	50 / M	1002628	8 MONTHS	-	-	-	-	-	-	-	N	N
92	SIVARAMAN	60 / M	1001503	4.7 YEARS	-	-	-	-	H2A	-	-	N	N
93	RENGASAMY	62 / M	1003110	2.2 YEARS	-	-	-	-	H2A	-	-	N	PYLORIC EROSIONS
94	SARAVANAN	35 / M	1003217	9 MONTHS	-	+	+	-	H2A	-	-	N	ANTRAL EROSIONS
95	MANI	60 / M	1002897	3 YEARS	-	+	-	-	H2A	-	+	N	PYLORIC ULCER
96	MITHEEN	60 / M	991911	8 MONTHS	+	+	+	-	H2A	+	-	N	PYLORIC EROSIONS
97	VEMBAIYAN	60 / M	993899	2.8 YEARS	-	-	-	-	H2A	-	-	N	N
98	MURUGAIYAN	60 / M	904701	1.7 YEARS	-	-	-	+	H2A	-	-	N	ANTRAL ULCER
99	ANANDHAN	65 / M	994921	3 YEARS	-	-	-	-	H2A	-	-	N	N
100	GOVINDHARAJ	50 / M	995649	1.4 YEARS	-	-	-	-	H2A	-	-	N	ANTRAL EROSIONS

N- NORMAL , + - PRESENT , - - ABSENT , H2A - H2 ANTAGONIST

Duodenum
ULCER
N
N
N
N
N
EROSIONS
N
EROSIONS
N
N
N
EROSIONS
N
EROSIONS
ULCER & EROSIONS
N
N
EROSIONS
N
N
N
ULCER
N
ULCER
N
N
N

N
N
N
N
N
N
N
ULCER
N
N
N
N
N
EROSIONS
N
N
N
N
EROSIONS
N
N
ULCER
N
N
N
N
EROSIONS
N
N
N
N
N
N
N
N
N
N
N
N
N

EROSIONS
N
N
N
N
N
EROSIONS
ULCER
N
N
N
N
N
N
N
N
N
N
N
ULCER
N
N
N
N
N
N
N
EROSIONS
N
EROSIONS
N
N