Research Article

Pathophysiological Mechanisms and Preclinical Models of Peptic Ulcer

R. Srinath and Atanu Banik

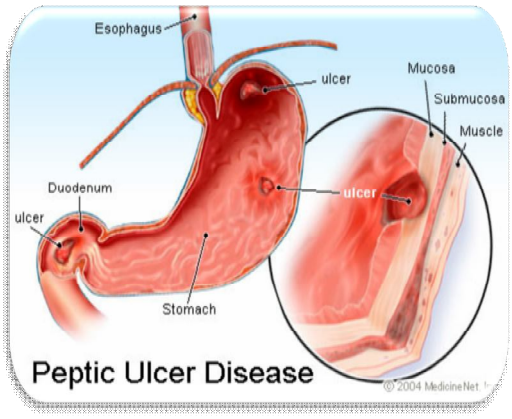
P.E.S College of Pharmacy, Hanumanthanagar, 50 feet road. Bangalore-560050, Karnataka, India.

ABSTRACT

A Peptic ulcer is a mucosal lesion of the stomach or duodenum in which the acid and pepsin play major pathogenic roles. The major forms of peptic ulcer are gastric ulcer and duodenal ulcer, both of which are chronic diseases often caused by ***Helicobacter pylori***. The term peptic ulcer also encompasses gastric ulcers and duodenal ulcers associated with stress or the ingestion of drugs, most commonly aspirin and non-steroidal anti-inflammatory drugs (NSAIDs). Ulcer associated with Zollinger-Ellison Syndrome (ZES), caused by gastrin secreting is also considered a form of peptic ulcer. Whether an ulcer develops, depends on the balance between aggressive factors (mainly gastric acid and pepsin) and factor that participate in mucosal defense or resistance to ulceration. Peptic ulcer develops when gastro duodenal mucosal defenses are unable to protect the epithelium from the corrosive effects of acid and pepsin. Gastric acid catalyses the cleavage of inactive pepsinogen molecules to proteolytically active pepsins and also provides the low pH for pepsin activity. Peptic ulcer effect of plant drugs and herbal formulations are studied against chemicals (ethanol, acetic acid, histamine), drugs (dimaprit, indomethacin, aspirin, reserpine) and stress induced ulcer in rats as they virtually mimic any form of occurring gastric ulcer in stomach. The level of pH, total acidity, ulcer index reflects damage to stomach mucus as well as protective effect of plant drugs.

INTRODUCTION

A peptic ulcer is a hole in the gut lining of the stomach, duodenum, or oesophagus. An ulcer occurs when the lining of these organs is corroded by the acidic digestive juices which are secreted by the stomach cells. A peptic ulcer of the stomach is called a gastric ulcer, of the duodenum, a duodenal ulcer; and of the esophagus, an esophageal ulcer[1].



TYPES OF PEPTIC ULCERS [2]

Peptic ulcers are the areas of degeneration and necrosis of GIT mucosa exposed to acid-peptic secretions. Though they can occur at any level of the alimentary tract that is exposed to Hcl and pepsin, They occur most commonly(98-99%) in either the duodenum or in the stomach in the ratio of 4:1 Each of the two main types may be acute or chronic.

Acute peptic ulcers or stress ulcers are multiple, small mucosal erosions, seen most commonly in the stomach but occasionally involve in the duodenum.

Pathogenesis

It is not clear how the mucosal erosions occour in stress ulcers because actual hyper secretion of gastric acid is demonstrable in only crushing's ulcers occurring from intracranial such as due to brain trauma, intracranial surgery and brain tumor. In all other etiologic factor, gastric acid secretion is normal or below normal .in these conditions the possible hypotheses for genesis of stress ulcers are as under:

1. Ischaemic hypoxic injury to the mucosal cell.
2. Depletion of the gastric mucus barrier rendering the mucosa susceptible to attack by acid-peptic secretion.

Chronic peptic ulcers i.e **gastric** and **duodenal ulcer**

Duodenal ulcers

There is conclusive evidence to support the role of high acid pepsin secretion in the causation of duodenal ulcers. Besides this, a

few other noteworthy features in the pathogenesis of duodenal ulcers are as follows:-

1. There is generally hyper secretion of gastric acid into the fasting stomach at night which is takes place under the influence of vagal stimulation. There is high basal as well as maximal acid output in response to various stimuli.
2. Patient of duodenal ulcer have rapid emptying so that the food which normally buffers and neutralise the gastric acid ,passes down into the small intestine, leaving the duodenal mucosa exposed to aggressive action of gastric acid.

Gastric ulcer[3]

Gastric ulceration is a commonly encountered clinical problem and occurs due to a disturbance of the delicate balance between HCL and mucosal resistance. Alteration in the activity of CNS ,peripheral neurotransmitters and autocoids as well as several chemical substance can increase H+ concentration resulting in ulcer formation.[3] The pathogenesis of gastric ulcer is mainly explained on the basis of impaired gastric mucosal defences against acid pepsin secretion some other features In the pathogenesis of gastric ulcer are as follows:-

1. Hyperacidity may occur in gastric ulcer due to increased serum gastrin level in response to ingested food in an atomic stomach.
2. However many patients of gastric ulcer have low to normal gastric level. Ulcerogenesis in such patients is explained on the basis of damaging influences of other factors such as gastritis, bile reflux, etc.
3. The normally protective gastric mucus barrier against acid pepsin is dearranged in gastric ulcer there is depletion in the quantity as well as quality of gastric mucus.

Distinguishing features of two major forms of peptic ulcer.[4]

Features	Duodenal ulcer	Gastric ulcer
1. Incidence	a. Four times more common than gastric ulcers and b. Usual age 25-50 years.	Less common than duodenal ulcers and Usually beyond 6th decade.
2. Etiology	Most commonly as a result of H.pylori infection and other factors-hyper secretion of acid-pepsin, association with alcoholic cirrhosis, tobacco, hyperparathyroidism, chronic pancreatitis, blood group O, genetic factors.	Gastric colonisation H.pylori asymptomatic but higher chances of development of duodenal ulcer. Disruption of mucus barrier most important factor. Association with gastritis, bile reflux, drugs, alcohol, tobacco.
3. Pathogenesis	Mucosal digestion from hyperacidity most significant factor. Protective mucus barrier may be damaged.	Usually normal to low acid levels Damage to mucus barrier significant factor.
4.Pathologic changes	(a). Most common in the first part of duodenum. (b).1-2.5 cm in size. round to oval.	(a) Most common along the lesser curvature and pyloric antrum. (b) Same to duodenal ulcer.
5.Clinical features	Pain-food-relief pattern Night pain common No vomiting No loss of weight No particular choice of diet Marked seasonal variation Occur more in people at greater stress.	Food-pain pattern No night pain Vomiting common loss of weight Patients choose bland diet devoid of curries No seasonal variation More often in labouring groups

CAUSES OF PEPTIC ULCER

●Helicobacter pylori (H. pylori)

H. pylori can cause either an antral predominant gastritis (associated with increased meal stimulated acid production), which predisposes to duodenal ulceration, or a corpus pre-dpminant or pan gastritis (associated with a low gastric acid production),which predisposes to gastric ulceration and distal gastric adenocarcinoma.[5,6] However, most people with H . pylori induced gastritis develop none of these clinical problem and remain asymptomatic.[6]

Pathogenesis

only about 15% of individuals infected with H.pylori ever develop a peptic ulcer: who develops disease depends on bacterial ,host and environmental factors. The best describe virulence determinants are expression of active form of a vacuolating cytotoxin (VacA)[7] and possession of a protein secretory apparatus called Cag(cytotoxin associated gene product) that stimulates the host

inflammatory response. Cag strain interact more closely with epithelial cells and induced release of pro inflammatory cytokines, thereby increasing inflammation. However it is unclear whether it is this or the direct translocation of a bacterial protein (CagA) into gastric epithelial cells that is the primary cause of disease, including gastric adenocarcinoma . Host genetic susceptibility and environmental factors also affect disease risk; for example ,smoking is strongly associated with peptic ulceration in H. pylori infected individuals.[8]
H.pylori induced duodenal ulceration arises in people with antral predominant gastritis[9] Hypergastrinaemia ,as a consequence of the antral inflammation, leads to an increased acid production from the proximal acid secreting areas of the stomach acid load in the duodenum is one factor encouraging duodenal ulceration.[10]

●Non-steroidal anti-inflammatory drugs (NSAIDs)

The use of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with the occurrence of de novo adverse digestive events,including gastric mucosal erosions, ulcers, bleeding and perforation, as well as an increased risk of severe complications from pre-existing chronic ulcers.[11] The pathophysiology of NSAID inducedgastric injury depends, at least in part, on their ability to decrease prostaglandin production through cyclooxygenase (COX) inhibition, and partly on COX independent mechanisms.[12] The combination of COX-dependent and COX-independent mechanisms leads to oxidative tissue injury, which seems to play a major role in the pathogenesis of NSAID-induced gastricdamage [13,14]. Consistently with this view, gastric mucosal levels of malondialdehyde (MDA), a product arising from tissue oxidation, have been found to increase following NSAID administration [15]. Moreover, gastric ulcer repair is highly regulated by growth factors [16].Amongthese, vascular endothelial growth factor (VEGF) promotes ulcer healing via stimulation of new microvessel formation, and indomethacin has been shown to interfere with this process through a down regulation of VEGF expression.[17]

●Zollinger–Ellison syndrome

The Zollinger-Ellison (ZE) syndrome is characterized by autonomous gastrin production by an adenoma or adenocarcinoma of the pancreas or duodenum. The Zollinger-Ellison syndrome is distinguished from peptic ulcer disease by the demonstration of fasting hypergastrinemia. There are many causes of fasting hypergastrinemia (gastritis, vagotomy and pyloroplasty, the short bowel syndrome, rheumatoid arthritis, retained antrum, G-cell hyperplasia), but only two conditions-atrophic gastritis and renal failure are associated with gastrin levels increased several times above the upper limit of the normal range. However, in a patient with peptic ulcer disease and hyper gastrinemia, it is important to exclude the Zollinger-Ellison syndrome. The Zollinger-Ellison syndrome arises from a gastrinoma, a tumour in the pancreas. This may be a localized or diffuse tumour. The presence of hyper gastrinemia leads to hyper secretion; while the maximal acid output may be increased, the major defect is basal hyper gastrinemia and a marked increase in the basal acid output. The patient will have aggressive peptic ulcer disease with ulceration in unusual sites or multiple ulcers that fail to heal on medical therapy. Hypertrophic gastric folds and diarrhoea may be prominent features.

●Hereditary factors

Hereditary factors are important in the pathogenesis of peptic ulcer disease, as suggested by a higher prevalence of peptic ulcer disease in certain genetic syndromes. A number of familial aggregations have been noted in patients with peptic ulcer disease. These include hyper pepsinogenemia 1, normal pepsinogenemia 1, antral G-cell hyper function, rapid gastric emptying, childhood duodenal ulcer and immunologic forms of peptic ulcer disease. Heredity also plays a role in the development of ulceration and is associated with the syndrome of multiple endocrine adenomatosis 1 (adenomas of the pancreas, pituitary and parathyroid). Parents, siblings and children of ulcer patients are more likely to have peptic ulcer disease than control individuals. There is greater concordance for ulcer disease in identical than in fraternal twins. Hyper pepsinogenemia 1 appears to be an autosomal dominant trait. There is increasing evidence to suggest that familial peptic ulcer disease is related to Helicobacter pylori infection amongst family members.

●Male sex

The male to female ratio for duodenal ulcers is about 3:1, and for gastric ulcers about 1.5 to 2.1.

●Cigarette smoking

Smoking is associated with a higher prevalence of peptic ulcer disease and may be associated with impaired healing of duodenal

and gastric ulcer disease. Also, death rates from peptic ulcer disease are higher in individuals who smoke. Smoking increases a person's risk of getting an ulcer because the nicotine in cigarettes causes the stomach to produce more acid. Cigarette smoking increases both the incidence and relapse rate of peptic ulcer diseases and also delays ulcer healing.

●Pepsinogen

Human gastric mucosa contains aspartic proteinases that can be separated electrophoreti-cally on the basis of their physical properties into two major groups: Pepsinogen I _PGA,PGI.; and Pepsinogen II _PGC, PGII.. Pepsinogens consist of a single polypeptide chainwith molecular weight of approximately 42 000 Da. Pepsinogens are mainly synthesized andsecreted by the gastric chief cells of the human stomach before being converted into theproteolytic enzyme pepsin, which is crucial for the digestive processes in the stomach.Pepsinogen synthesis and secretion are regulated by positive and negative feed-backmechanisms. In the resting state pepsinogens are stored in granules, which inhibit further
synthesis. After appropriate physiological or external chemical stimuli, pepsinogens aresecreted in the stomach lumen where hydrochloric acid, secreted by the parietal cells,converts them into the corresponding active enzyme pepsins. The stimulus-secreting couplingmechanisms of pepsinogens appear to include at least two major pathways: oneinvolving cAMP as a mediator, the other involving modification of intracellular Ca2qconcentration. Physiological or external chemical stimuli acting through the intracellular metabolic adenyl cyclase are more effective in inducing ‘de no¨o’ pepsinogen synthesis than those acting through intracellular Ca2q. The activation of protein kinase C _PK-C. would
appear to be involved in regulatory processes. The measurement of pepsinogens A and C in the serum is considered to be one of the non-invasive biochemical markers for monitoring
peptic secretion and obtaining information on the gastric mucosa status of healthy subjects. Recently, pepsinogen measurements have been used as an effective biochemical method for evaluating and monitoring patients with gastrointestinal diseases and for checking the effects of drug treatment. The level of PGA in the serum is always high in normal gastritis,
while in atrophic gastritis it is always low. In both cases the PGC level in the serum is high. In most gastrointestinal pathologies the ratio between the PGArPGC decreases. Various reports concerning hormone andror enzyme modification as well as gastrointestinal distress in the case of long distance exercise have been reported. It has been suggested that the origin of the gastrointestinal distress experienced by long distance runners is a transient ischaemia of the gastric mucosa; it is also suggested that a hypobaric]hypoxic environment could contribute to induce gastric mucosa necrosis. Interrelation between gastrointestinal distress, hypobaric]hypoxic environment and modifications of PGA and PGC, gastrin and cortisol was evaluated in 13 athletes after a marathon performed at 4300 m. Gastrointestinal symptoms occurred in approximately 40% of the athletes. After the race the athletes showed a significant increase of gastrin and cortisol, while the ratio between PGArPGC decreased. No relationship was observed between gastrointestinal symptoms and hormonal changes after the race.[18]

●Alcoholic cirrhosis

Ulcers are more common in people who have cirrhosis of the liver. Since cirrhosis of the liver is associated with alcohol consumption, alcohol reduction may work as a preventive measure to reduce the risk of peptic ulcer. Also alcohol is thought to slow wound healing increasing the risk of bleeding ulcers. Consumption of alcohol significantly increases the risk of gastric ulcers.

●COX-2 inhibitors

The cyclo-oxygenase-2 (COX-2) inhibitors exert their therapeutic effect by inhibiting the production of prostaglandins involved in inflammation. At therapeutic doses they have little or no inhibitory effect on cyclo-oxygenase-1, which is expressed in many tissues and is necessary for the production of prostaglandins that protect the mucosa of the upper gastrointestinal tract. It is therefore expected that COX-2 inhibitors will have reduced gastro duodenal toxicity compared with conventional NSAIDs. Cyclo-oxygenase-2 (COX-2) inhibitors cause gastro duodenal ulceration and subsequent complications. The risk, however, is halved compared with conventional non-steroidal anti-inflammatory agents (NSAIDs). COX-2 inhibitors, like NSAIDs, may exacerbate inflammatory bowel disease and cause intestinal strictures.

●COPD

Gastrointestinal symptoms could be related to the high incidence of peptic ulcer disease in patients with Chronic obstructive pulmonary diseases (COPD), to abdominal discomfort caused by bronchodilator drugs or

corticosteroids, or to early satiety caused by flattened diaphragm or air swallowing.

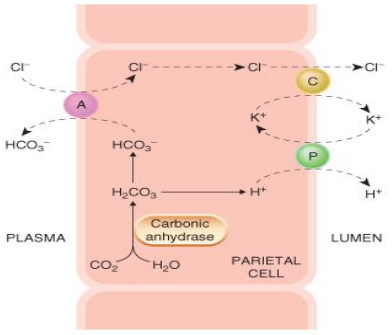
●Corticosteroids

Glucocorticoids increase the secretion of hydrochloric acid, pepsinogen and pancreatic trypsinogen. They increase both basal and nocturnal gastric secretion. They decrease the resistance of gastric mucosa to the irritant action of the gastric secretions, and produce or aggravate gastric ulceration. They are ulcerogenic; the risk is doubled, bleeding and silent perforation of ulcers may occur.

The regulation of acid secretion by parietal cells.[19]

The regulation of acid secretion by parietal cells is especially important in peptic ulcer and constitutes a particular target for drug action. The secretion of the parietal cells is an isotonic solution of HCl (150 mmol/l) with a pH less than 1, the concentration of H^+ being more than a million times higher than that of the plasma. The Cl^- is actively transported into canaliculi in the cells which communicate with the lumen of the gastric glands and thus with the lumen of the stomach. This Cl^- secretion is accompanied by K^+ through Cl^- /k channel , H^+ proton is tansported by a K^+/H^+-ATPase (proton pump) into lumen while k enters the cell .

Carbonic anhydrase catalyses the combination of carbon dioxide and water to give carbonic acid, which dissociates into H^+ and bicarbonate ions. The HCO3 exchanges across the basal membrane for Cl^- via.. Cl/ HCO3 antiporters .HCO3 diffuses into blood



Three main stimuli act on the parietal cells:

1) gastrin (a hormone)
2) acetylcholine (a neurotransmitter)
3) histamine (a local hormone).

The parietal cells operate in close association with another type of cell called enterochromaffin like cells (ECL cells), the primary function of which is to secrete histamine, that act on H 2 receptor.The rate of formation and secretion of hydrochloric acid by the parietal cells is directly related to the amount of histamine secreted by the ECL cell.

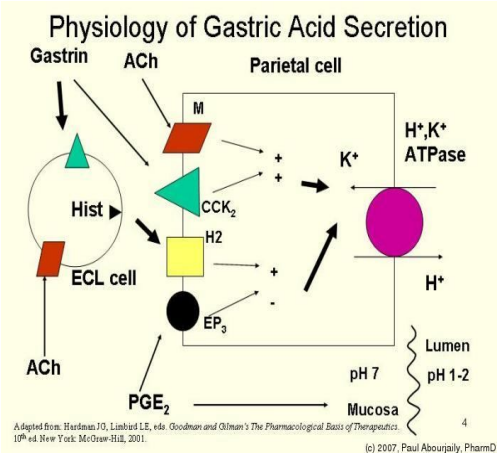
The ECL cells is stimulated by-

(i) the hormonal substance gastrin,

(ii) In addition, the ECL cells can be stimulated by acetylcholine released from stomach vagal nerve endings.

Gastrin Is stimulated by amino acid and small peptides, which act directly on the gastrin-secreting cells.

Acetylcholine is released from neurons and stimulates specific muscarinic receptors on the surface of the parietal cells and on the surface of histamine-containing cells, When receptors in parietal cell is activated cyclic AMP & calcium are released which then activate h+/k+ atpase resulting in proton secretion.



Approaches for the treatment of peptic ulcer[20]

Reduction of gastric acid secretion

a) H2 antihistamine: Cimitidine, Ranitidine, Famotidine, Roxatidine.
b) Proton pump inhibitor: Omeprazole,Lan-soprazole,Pantoprazole,Rabiprazole.
c) Anticholinergics: Pirenzepine, Propentheline,Oxyphenonium.
d) Prostaglandin analouge: Misoprostol

Neutralization of gastric acid(Antacids)

a) Systemic: Sodium bicarbonate,Sod.citrate.
b) Nonsystemic: magnesium hydroxide, Mag.trisilicate, Alluminium hydroxide gel, Cal. carbonate.

Ulcer protective: Sucralfate,Colloidal bismath subcitrate(CBS)

Anti-H. pylori drugs: Amoxicilline,Clarithro-mycin,Metronidazole,Tinidazole,Tetracycline

How agent suppress gastric acid secretion[20,21]

Proton Pump Inhibitor

These are prodrug need to activate in an acid environment. These agent enter the parital cell from blood and because of their weak basic nature, accumalate in the acidic secretory canaliculi of the parital cell, where it forms sulfenic acid. This activated form reacts by binding with sulfhydryl group of cystein of H+,K+ ATPase and reduce acid secretion.

H2 Receptor Antagonist

Its binds with H2 receptor on the basolateral membrane of parital cell and inhibit cAMP which leads to inhibition of ca+ formation and inactivation of H^+K^+ ATPase pump.

Prostaglandin Analouge

PGE2 & PGI2 are the major PG synthesized by the gastric mucosa, they inhibit acid production by binding to the EP3 receptor on parital cell. Its inhibit adenyl cyclase and decreased levels of intracellular cAMP.

Antacids

These are basic substance which neutralize gastric acid and raise pH of gastric contents. Peptic activity is indirectly reduced if the pH rise above 4, because pepsin is secreted as a complex with an inhibitory terminal moiety that dissociates below pH 5, optimum peptic activity is exerted between pH 2 to 4. Antacids do not decrease the acid production; the potency of an antacids is generally expressed in terms of its acid neutralizing capacity, which is defined as number of mEq of 1N Hcl that are bought to pH 3.5 in 15 min by a unit dose of antacid preparation.

Sucralfate

Sucralfate consist of the octasulfate of sucrose to which aluminium hydroxide has been added. In an acid environment it undergoes extensive cross-linking and polymerization to produce a viscous, sticky gel that adhere strongly to epithelial cells and even more strongly to ulcer craters for as long as 6 hrs after a single dose. Sucralfate have cytoprotective activity including stimulation of local production of PG and epidermal growth factor(EGF).It still may be usefull in the prophylaxis of stress ulcer

Adverse drug reactions of antiulcer agents[21]

Proton pump inhibitor

Its inhibit the activity of some hepatic cytochrome P450 enzymes therefore may decrease the clearance of benzodiazepines, warfarin, phenytoin, and many other drugs. Apart from that its also causes for nausea, vomiting, abdominal pain, constipation and diarrohea are the most common side effect. Chronic treatment with omeprazole decrease the absorption of vit $B_{12.}$

H_2 receptor antagonist

Side effect are usually minor and include diarrhea, headache, drowsiness, fatigue, mascular pain, and constipation. In CNS-confusion, delirium, hallucination, slurred speech.

Gynecomastia in men and galactorrhea in woman may occur due to binding of cemetidine to androgen receptor and inhibition of the cytochrome P450 catalysed hydroxylation of estradiol.

Prostaglandins analogue

Most frequent side effect of misiprostol is diarrhea with or without abdominal pain and cramps. During pregnancy it causes abortion by increasing uterine contractility.

Sucralfate

Most common side effect is constipation .Aluminum containing antacids should not give to the patient with renal failure. Its produce strong layer in stomach so its reduces the absorption of other drug.

Various methods for inducing gastric ulcer in rats[22,23]

various methods-

1) Pylorus ligation in rats(SHAY MODEL)[24]
2) Indomethacin induced ulcer in rats.[24]
3) Ethanol induced mucosal damage in rats
4) Histamine induced gastric ulcers.[25]
5) Dimaprit induced duodinal ulcers
6) Stress ulcer through immobilization stress
7) Acetic acid induced gastric ulcers
8) Gastric ischemia-reperfusion injury in rats
9) Reserpine induced gastric ulcer
10) Subacute gastric ulcer in rats
11)Restraint ulcers in rats.[25]

1) Pylorus ligation in rats (shay rat)

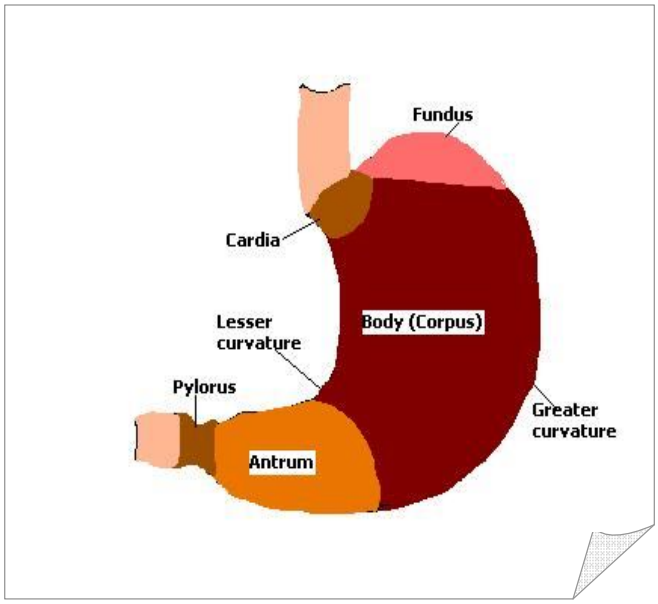
Purpose and Rationale

A simple and reliable method for production of gastric ulceration in the rat based on ligature of the pylorus has been published by Shay et al. (1945).The ulceration is caused by accumalation of acidic gastric juice in the stomach.

Procedure

Female Wistar rats (150-180g) are kept in fasting for 48 hour (only water has given). During this time all the rats were kept in single cages to avoid cannibalism. Ten animals are used per dose and as controls. Under ether anesthesia a midline abdominal incision is

made. The pylorus is ligated, care being taken that neither damage to the blood supply nor traction on the pylorus occurs. The abdominal wall is closed by sutures. The test compound are given by orally or by SC. About 17-19 hrs after pyloric ligation, the animals are sacrificed in CO2 anesthesia .The abdomen is opened and a ligature is placed around the esophagus close to the diaphragm. The stomach is removed and the content are drained in a centrifuge tube. Later stomach is opened and pinned on a cork plate, mucous examined with stereo microscope. The number of ulcer is noted and the severity recorded with the following scores: O= no ulcer, 1= superficial ulcer, 2=deep ulcer, 3=perforation The volume of the gastric content is measured. After centrifugation, acidity is determined by tit. With 0.1 N NaOH.



Evaluation

An ulcer index U1 is calculated:

$U1 = UN + US + UP \times 10^{-1}$

UN= average of no of ulcer per animals

US= average of severity scores

UP= % of animals with ulcers

UI & gastric acidity content of treated animals are compared with control.ID50 value can be calculated by probit analysis.

2) Indomethacin induced ulcer in rats

Purpose and rationale

NSAIDs like indomethacin and acetyl-salicylic acid, induced gastric lesions in man and in experimental animals by inhibition of gastric cyclo-oxygenase resulting in less formation of prostacyclin, the predominant prostanoids produced in the gastric mucosa.

Procedure

Groups of 8-10 Wistar rats weighing 150-200g are used.The test drugs are administered orally in 0.1% Tween 80 solution 10 min prior to oral indomethacin in a dose of 20 mg/kg6 hrs later, the rats are sacrificed in CO2 anesthesia and their stomachs removed. Formal-saline(2%v/v) is then injected into the totally ligated stomachs for storage overnight.The next day, the stomachs are opened along the greater curvature, then washed in warm water, and examined under a 3-fold magnifier.The length of the longest diameters of the lessions are measured and summated to give a total lesion score(in mm) for each animal,the mean count for each group being calculated.

Evaluation

The mean score in control rats is about 25 (range 20-28).Inhibition of the lesion production is expressed as percentage value.

3) Stress ulcer through immobilization stress

Purpose and rationale

Psychogenic factors,such as stress, play a mojor role in the pathogenesis of gastric ulcers in man.Selye for the first time, described the

use of resistant for the production of gastric ulcer.

Procedure

Wistar rats are fasted for 24 hrs before the experiment.After oral or s.c administration of the test drug or the placebo solution the animals are slightly anaesthetized with etherBoth lower and upper extremities are fixed together and the animal are wrapped in wire gaze. They are horizontally suspended in the dark at 20ºC for 24 hrs and finally sacrificed in CO2 anesthesia.The stomac is removed and fixed on a cork plate and the number and severity of ulcers is registered with a stereomicroscope using the following scores:0=no ulcer; 1=superficial U; 2=deep U; 3=perforation

Evaluation

An ulcer index UI is calculated:

$U1 = UN + US + UP \times 10^{-1}$

UN= average of no of ulcer per animals

US= average of severiaty scores

UP= % of animals with ulcers

4) Dimaprit induced duodinal ulcers

Purpose and rationale

Dimaprit, an H2 receptor agonist,has been shown to induce gastric erosions in rats after a single I.V dose and duodinal ulcers in guinea pigs after repeated S.C doses. The model is especially useful for screening of H2 –blocker.

Procedure

Sprague Dawley rats or guinea pig are used for the experiment. The animals are fasted for 24 hrs before the experiment. Then test drug is given orally and 1 hr later dimaprit also given (100mg/kg) by I.V route single dose. Then the animals are sacrificed 1 hr after the dimaprit injection and stomach and duodinum are examined for lesions.

Evaluation

An ulcer index UI is calculated:

$U1 = UN + US + UP \times 10^{-1}$

UN= average of no of ulcer per animals

US= average of severiaty scores

UP= % of animals with ulcers

5) Ethanol induced mucosal damage (cytoprotective activity)

Purpose and rationale

Intragastric application of absolute ethanol is a reproducible method to produce gastric lesions in experimental animals. Using a transmission densitometer, it is possible to quantify
the extent of gastric lesions induced by ethanol, by measuring the optical density of photographic negatives of gastric mucosa.

Procedure

Wister rats are fasted for 24 hrs before the operative procedure ,having access to drinking water .Now the test drug (cytoprotective drug prostanoid) or the vehicle is given to the animals orally. After 30 min 1 ml of absolute ethanol is given orally. The animals are sacrificed 1 hr later and stomach dissected out. The stomach are then opened, washed and ulcer severity grading done. Photograph of the tissues are taken and the negatives are examined under light densitometer. damaged areas have lower optical values.

Evaluation

The significance of difference in optical density b/w control & ethanol treated tissue is evaluate by student's t-test.

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