The Gastroprotective Effect of Proton Pump Inhibitors on Ethanol - Induced Gastric Erosion in Rats

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Abstract

Peptic ulcer diseases are one of the wide spread diseases. The causes of peptic ulcer diseases are increases gastric acid secretion. Studies focusing on the harmful effect of intra-gastric administration of ethanol which results in gastric mucosal injury, characterized by mucosal edema, sub-epithelial hemorrhage and inflammatory cell infiltration. Omeprazole and pantoprazole are proton pump inhibitors used in the treatment of gastric ulcer and gastroesophageal disease that inhibit gastric acid secretion by blocking the H+/K+- adenosine triphosphate enzyme. The present study was carried out to determine the anti-ulcer activity of proton pump inhibitors (omeprazole 10mg/kg and pantoprazole 3 mg/kg) on ethanol- induced ulcer rat model. Healthy *Sprague Dawley* rats with 12-14 weeks of age of either sex weighing between 150-200 gm. were used for present study. The animals were divided into three groups six animals in each .The ulcer was induced by administering ethanol 50% orally and the treated groups was drenched 10mg/kg omeprazole and pantoprazole 3mg/kg. The anti-ulcer activity of omeprazole and pantoprazole was able to protect against ulcer formation by ethanol was indicated by a decrease in ulcer index of both treated groups. From this study it can be concluded that omeprazole and pantoprazole possess anti-ulcerogenic activity. Besides , omeprazole might be better than pantoprazole in protection against ethanol- induced ulcer.

التأثير الإتقائي لمثبطات مضخة البروتون في القرحة المعدية المستحثَة بالإيثانول في الجرذان

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كلمات المفتاح :- الايثانول ، القرحة ، الاوميبرازول ، البانتوبرازول ، الجرذان.

الخلاصة

تعد القرحة المعدية واحدا من الامراض الواسعة الانتشار ، وان اسباب هذا المرض هو الزيادة المفرطة في الاحماض المعدية المفرزة والمؤدية لحدوث المرض. لقد ركزت الدراسات والبحوث التي اجريت في هذا المجال على التأثيرات المضرة للايثانول والتلف الذي يسببه في مخاطية المعدة والمتمثل بالوذمة المخاطية والنزف تحت البطانة والارتشاح للخلايا الالتهابية.

استخدمت الكثير من الادوية المضادة للقرح المعدية وامراض المرئ الناتجة من ارتفاع الحموضة وقد استخدمت الادوية التالية في دراستنا وهي الاوميبرازول والبانتوبرازول وهما من مجموعة الادوية التي تعمل كمثبطات لمضخات البروتون.

اجريت هذه الدراسة للتحقق من التاثيرات المضادة للقرح المعدية للادوية قيد الدراسة وذلك باستخدام الحيوانات المختبرية (الجرذان) كموديل، حيث استحدثت القرحة المعدية فيها بواسطة الايثانول. استخدمت الجرذان المهقاء بعمر 12-14 اسبوع من كلا الجنسين وبمعدل وزن يتراوح بين 150-200 غم . قسمت الحيوانات الى مجاميع ثلاث وبواقع ست حيوانات للمجموعة الواحدة .

استحدثت القرحة المعدية في المجاميع الثلاثةباستخدام الايثانول بتركيز 50% وبجرعة 10مل/ كغم عن طريق الفمفيما جرعت مجاميع المعاملة دواء الاوميبرازول و البانتوبرازول بجرعة 10 ملغ/كغم و 3ملغ/كغم على التعاقب قبل ساعة من اعطائها الايثانول.

اشارت نتائج الدراسة الى امكانية الادوية قيد الدراسة من توفير الحماية اللازمة لمواجهة تكون القرح المعدية في الجرذان المجرعة بالايثانول و كان ذلك واضحا من خلال الانخفاض الواضح في دليل التقرح بكلا مجموعتي المعالجة مقارنة مع مجموعة السيطرة .

يمكننا ان نخلص من هذه الدراسة الى امتلاك الاوميبرازول و البانتوبرازول الفعالية المضادة للتقرح والذي ربما يعزى الى الفعالية المضادة لافراز الحامض المعدي والتي كانت نتائجه لصالح الاوميبرازول عند مقارنته بالبانتوبرازول كما هو موضح في نسب الحماية من القرح المعدية.

Introduction

Ethanol consumption is considered to be a risk factor in the development of gastro-duodenal ulcers. Intra-gastrically administered ethanol rapidly penetrates the gastrointestinal mucosa, causing membrane damage, exfoliation of cells and erosion. The subsequent increase in mucosal permeability together with the release of vasoactive products from mast cells, macrophages and blood cells may lead to vascular injury, necrosis and ulcer formation (1).

Generation of free radicals has also been suggested as one of the mechanisms responsible for ethanol-induced gastro-duodenal injury(2).The stomach and upper gastrointestinal tract are the main sites of ethanol metabolism and the gastric mucosa is rich in xanthine oxidase that is capable of metabolizing acetaldehyde to acetate, accompanied by the generation of free radicals (3). Lipid peroxidation mediated by oxygen free radicals is believed to be an important cause of the destruction and damage to cell membranes, which has been demonstrated to play an important role in the pathogenesis of gastric mucosal injury induced by ethanol (4).

Potassium channels represent the largest and most diverse family of ion channels in the body. ATP-dependent K^+ channels (K_{ATP}) are a class of ligand gated proteins. They have been postulated to be involved in a variety of physiologic functions of the stomach such as gastric blood flow regulation, acid secretion and stomach contractility (5).

Gastric erosions have been defined as endoscopically detectable mucosal breaks that do not penetrate the muscularis mucosa (6).The duration of erosion can be short-term, chronic or recurrent (7).

The etiology of gastric erosions of indeterminate duration has been postulated to involve Herpes simplex virus (HSV), *Helicobacter pylori* (*H-pylori*) ,the use of non-steroidal anti-inflammatory drugs (NSAIDs), hyperacidity, and use of alcohol and cigarette smoking(8).

The usual finding is a white base of erosion, although occasionally a blackened base may be seen as a mark of recent hemorrhage; the lesions are flat or minimally depressed and usually are surrounded by a narrow rim of erythema.

Alcohol causes the stomach cells to over secrete both acid and histamine which make the stomach linings vulnerable to ulcer formation.Ethanol also reduces prostaglandin (PG) levels, increases the influx of calcium ions (9).

Ethanol also produces a marked contraction of the circular muscles of fundic strip. Such a contraction can lead to mucosal compression at the site of the greatest mechanical stress, at the crests of mucosal folds leading to necrosis and ulceration. This reduces the secretion of bicarbonates and production of mucus and also leads to increased neutrophil infiltration into the gastric mucosa. These neutrophils adheres to endothelial cells, thereby blocking capillaries and induce damage to the endothelial cells through the release of proteases, leukotriene (LTC_4) and oxygen free radicals (10).

Ethanol – induced gastric damage is mediated by the generation of free radicals based on the finding that ethanol administration apparently elevates the lipid peroxide levels in gastric mucosa and depletes the major antioxidant factors , including enzymes such as superoxide dismutase , catalase and glutathione (GSH) peroxidase as well as non-enzymatic antioxidants such as reduced GSH and vitamins A , C , and E (11).

The proton pump inhibitors are prodrugs with an acid-resistant enteric coating to protect them from premature degradation by gastric acid. The coating is removed in the alkaline duodenum and the

prodrug a weak base is absorbed and transported to the parietal cell canaliculus. There, it is converted to the active form that bind to the hydrogen / potassium adenosine triphosphate enzyme system (H^+/K^+-ATPase) of the parietal cell, thereby suppressing secretion of hydrogen ions into the gastric lumen. The membrane-bound proton pump is the final step in the secretion of gastric acid (12).

Omeprazole and pantoprazole show an ulcer healing effect by inhibiting neutrophil chemotaxis , superoxide production , release of active oxygen metabolites and decrease pepsin damage to gastric mucosa .Cytoprotective effect of omeprazole is due to increased expression of cyclooxygenase-2 (COX-2) protein and elevating the levels of PGE_2 (13).

Materials and Methods

Healthy *Sprague Dawley* rats with 12-14 weeks of age of either sex weighing between 150-200 gm. were used for present study. The animals were kept in plastic ideal cages in the animal house of the pharmacology department - college of pharmacy at university of Kerbala. The animals were accommodated for a week. They were maintained in standard conditions at room temperature and relative humidity at 60± 5% for 12 hours light dark cycle. They have been given standard pellet diet supplied by Al- hafidh factory for fodder and the water was supplied ad-libitum throughout the course of study. The experiments were approved by the Animal Ethical Committee university of Kerbala.

The animals were divided into three groups six animals in each . The ulcer was induced by administering ethanol. In order to induce ulcer by ethanol all the animals were fasted for 24 hours before administration of ethanol.

All groups received ethanol (50 % v/v) (in distilled water) in a dose of 10 mL/kg orally via a stainless steel intubation needle (14).

The groups were divided as follows:-

Group I- control:- Received ethanol (50% v/v) 10 mL/ kg orally.
Group II- Omeprazole 10 mg/kg 1 hour before ethanol administration.
Group III- Pantoprazole 3 mg/kg 1 hour before ethanol administration.

Two hours after ethanol administration, all rats were killed by an overdose of chloroform and the stomachs were rapidly removed, opened along their greater curvature and gently rinsed under running tap water and spread on a paraffin plate. Lesions in the glandular part of the stomach were examined under dissecting microscope. The groups were divided as the followings

Scoring of Ulcer

Scoring of ulcer would be made as follows:
0= normal stomach, 0.5=red coloration, 1= spot ulcer, 1.5= hemorrhagic streak
2= ulcers, 3= perforation.
Mean ulcer score-(the mean of score of ulceration in the field of stomach under dissecting microscope)-for each animal will be expressed as ulcer index (UI)
Percentage protection= (control mean ulcer index – Test mean ulcer index)/control mean ulcer index × 100.(15).

Laboratory Tests

1- After the animals were deeply anesthetized 5ml of blood was withdrawn by cardiac puncture. Blood samples were immediately transferred to the vial containing ethylene di-amine tetra-acetic acid (EDTA) as anticoagulant for laboratory examinations [hemoglobin (Hb), erythrocyte sedimentation rate (ESR) and packed cell volume (PCV)].
2- The ESR, PCV and Hb were determined according to Wintrobe's method (16).

3- The gastric juice was removed and collected in a test tube, the material was centrifuged and the supernatant was examined for pH by pH meter.

Tissue Preparation

Stomachs were rapidly excised. The organs were washed briefly with tab water and then preserved in buffered formalin for histological examination.

Statistical Analysis

The experimental design used for such study was Rationalized Complete Block Design (RCBD). The results were reported as means ± standard error (SE). Unpaired t-test was used and the statistical differenceswere considered significant if the P value was less or equal to 0.05.

Results and discussion:-

Table (1) : illustrate the studied parameters (ESR, Hb, PCV, pH) values (in mean ± SE) for six observations.

Table (2): illustrate the protection percentage values of omeprazole and pantoprazole (in mean ± SE) for six observations.

Histological Results

Histological changes were shown as follows:-

Image 1 (Control):-shows the esophageal and gastric mucosa with well-defined focus of gastric ulcer with mixed chronic inflammatory cellular infiltration rich in lymphocyte (**black arrows**).

Image 2 (Control):-shows the gastric mucosa with well-defined focal erosions (**black arrow**) and no significant inflammation was seen.

Image 3 and image 4 (Omeprazole and pantoprazole respectively):-shows the gastric mucosa with intact epithelial layer (**black arrows**) and no erosions or ulceration could be seen, but there is some necrosis with pantaprazolehistological picture (**wide black arrow**).

Gastric ulcer is known as damage of the mucosal integrity of the stomach and duodenum defect produced due to active inflammation (17). Some noxious agents like (acid, pepsin, bile acids, pancreatic enzymes, drugs and bacteria) attacking on the gastro-duodenal mucosa by a host of integrity is maintained by an intricate system that provides mucosal defense and repair. (18).

Ethanol-induced gastric ulceration (EIGU) is considered to be an appropriate experimental model to study the pathogenesis of gastric mucosal ulceration. The mechanisms of EIGU are not fully understood. Gastric mucosal and sub-mucosal microcirculatory changes have been implicated in the pathogenesis of gastric ulceration (19, 20). Many investigators believed that gastric sub-mucosal microcirculatory disturbance is the main cause of EIGU (21).

Mucosal ischemia triggers gastric ulcer by inducing tissue necrosis, free radical formation and cessation of nutrient transport ; all resulting from vascular and microvascular injury such as thrombi, constriction or other occlusions. Increase in mucosal blood flow occurs as a response to gastric mucosal exposure to an irritant or when acid back-diffusion occurs. Ethanol has a direct noxious action on gastric mucosa(22).

Our histologic analysis showed that the grossly evident areas of mucosal damage consisted of regions of epithelial necrosis extending focally to the muscularis mucosa with associated vascular

dilatation and stasis, hemorrhage and edema (image 1). Occasional areas of injury also exhibited focal infiltration of neutrophils and this result is agreed with another study Robert et al (1979)[23]

The stomach and the upper GI tract are the main sites of ethanol metabolism. The metabolism of ethanol generates superoxide radicals which may in turn promote lipid peroxidation (24).

Ethanol also produces a marked contraction of the circular muscles of fundic strip. Such a contraction can lead to mucosal compression at the site of the greatest mechanical stress, at the crests of mucosal folds leading to necrosis and ulceration. This reduces the secretion of bicarbonates and production of mucus and also leads to increased neutrophil infiltration into the gastric mucosa as it appears in our results .These neutrophils adheres to endothelial cells, thereby blocking capillaries and induce damage to the endothelial cells through the release of proteases, leukotriene (LTC4) and oxygen free radicals (10).

Our laboratory results revealed little changes in PCV , ESR and Hb values. Because upper GI bleeding result from a very high concentration or long periods consumption of ethanol , in our study the dose of ethanol given to the rats just cause acute gastric mucosal damage , little hemorrhagic streaks and GI bleeding not occur severly.

Results of the present study documented that ethanol increases gastric acidity significantly which seemed to be as important as the damage induced by ethanol itself in promoting lipid peroxidation and neutrophil infiltration; the significant correlation between the suppression of acidity and UI values demonstrated this quality. Thus, it can be suggested that treatment with agents that have both antioxidant and anti-secretary properties (such as PPIs and H2 antagonists) affords the best protection against ethanol-induced gastric damage (25).

In ethanol model , PPIs (omeprazole and pantoprazole) significantly decrease the gastric acid and pepsin output indicating decrease in offensive acid and pepsin secretion. On the defensive factors, PPIs significantly increased the gastric mucin secretion and prevented the gastric mucosal damage induced by ethanol . Among these PPIs, pantoprazole showed better reduction of gastric acid secretion than to omeprazole . This effect of pantoprazole may be due to rapid onset of H+/K+ ATPase pump inhibition and a greater effect on intra-gastric pH as compared to omeprazole but our results revealed the opposite that omeprazole show better reduction of gastric acid secretion than pantoprazole; this may be due to difference in the manufacturing company of the drugs(TAD company ,Germany), and this result is supported by the protection percentage which is high in omeprazole treated group. Cytoprotective effect of omeprazole is due to increased expression of COX-2 protein and elevating the levels of PGE2. It also showed increased gastric pH and reduction in gastric acid secretion, which may be due to inhibition of gastric mucosa enzymes, carbonic anhydrase II (CA) and CA IV, which are located in abundance in the gastric parietal cells and in the secretory canaliculi walls. This inhibition potentiates the inhibitory effect on the proton pump. Similarly pantoprazole exerts its gastroprotective effects by increased bioavailability of mucosal sulfhydryl compounds and possibly PG (26).

Results of our study wereagree with the study of Sener et al. (2001)[25] and Robert et al (1979)[23]studies in that intragastric administration of ethanol consistently caused hemorrhagic lesions in the mucosa of the stomach and pretreatment of rats with omeprazole prevented the gastric ulcerogenesis significantly and decreased the UI values, while they disagree with Blandizzi, et al. (2000)[27]study in which pantoprazole provide more protection than omeprazole while our study proved the contrary.

Conclusions:-

It can be concluded that omeprazole and pantoprazole possess anti-ulcerogenic activityagainst ethanol –induced gastric ulcer

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Table (1) : The studied parameters (ESR, Hb, PCV, pH) values (in mean ± SE) for six observations.

Groups	Hb g/dL	ESR mm/hr	PCV %	pH
Control(ethanol)	12.2 ± 1.8	2 ± 0.4	38 ± 4.2	2.7 ± 0.1
Omeprazole (10 mg/kg)	13.6 ± 0.9	2.4 ± 0.6	44.1 ± 0.8	6.8 ± 0.3*
Pantoprazole (3 mg/kg)	12.3 ± 0.4	2.3 ± 0.3	40 ± 1.2	6.6 ± 0.5 *

*The mean differences are significant ($p< 0.05$) for both treated groups compared to control group.

Table (2.): The protection percentage values of omeprazole and pantoprazole (in mean ± SE) for six observations.

Groups	Mean ulcer index	% protection
Control (ethanol 50%)	1.35± 0.07	
Omeprazole(10 mg/kg)	0.1± 0.1*	93
Pantoprazole (3 mg/kg)	0.3± 0.1*	76

*The mean differences are significant ($p< 0.01$) for both treated groups compared to control group.

Histological Results

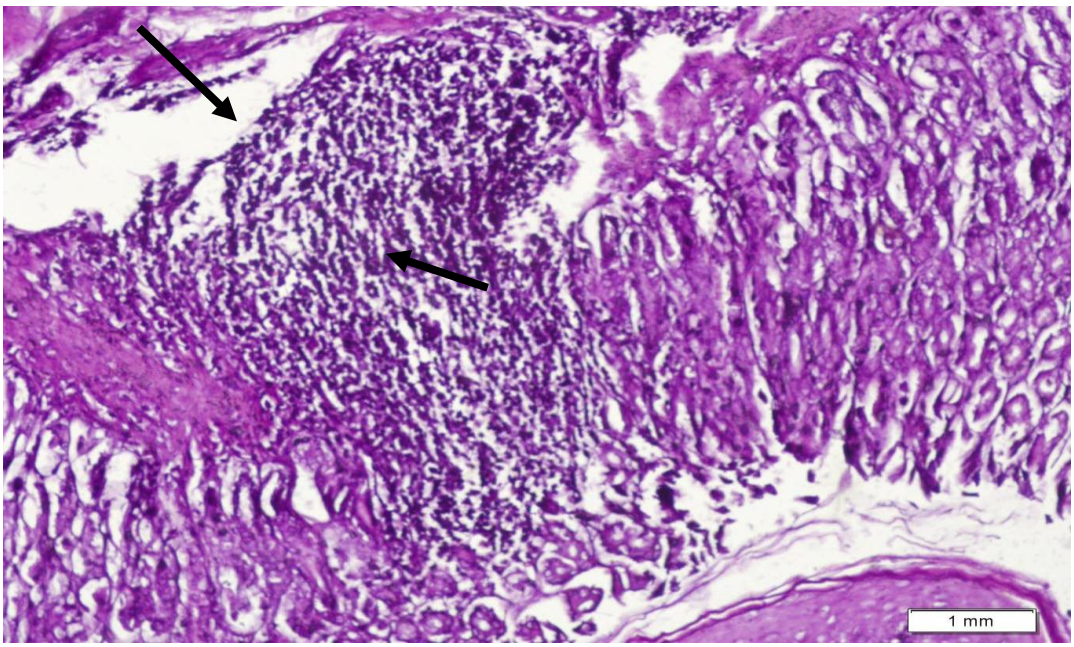

Image 1:- Histological section in stomach (group I- control, ethanol 50% v/v, x200), Hematoxylin and eosin stain (H & E)

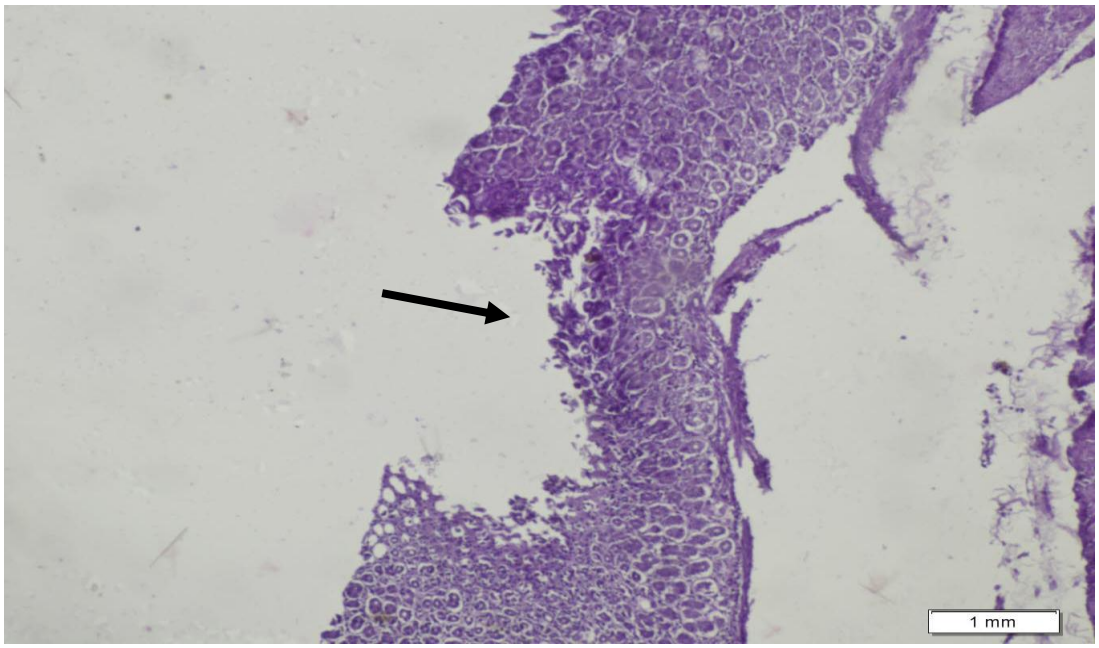

Image 2:- Histological section in stomach (group I- control, ethanol 50% v/v, x200), Hematoxylin and eosin stain (H & E)

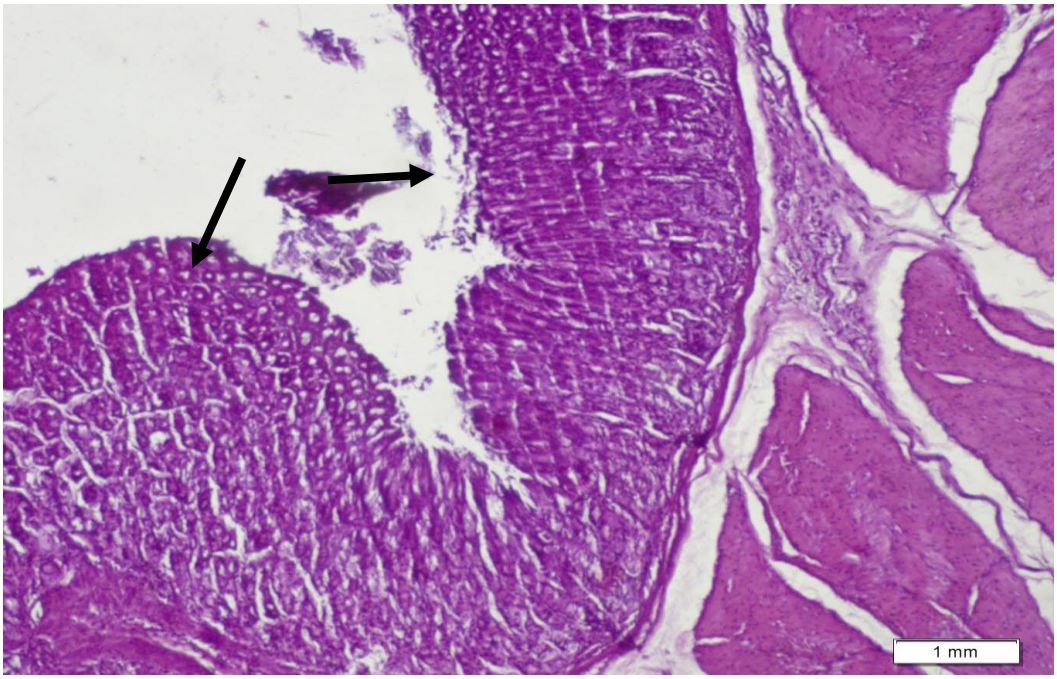

Image 3:- Histological section in stomach (group II-omeprazole , 10 mg/kg , x200 , H&E stain).

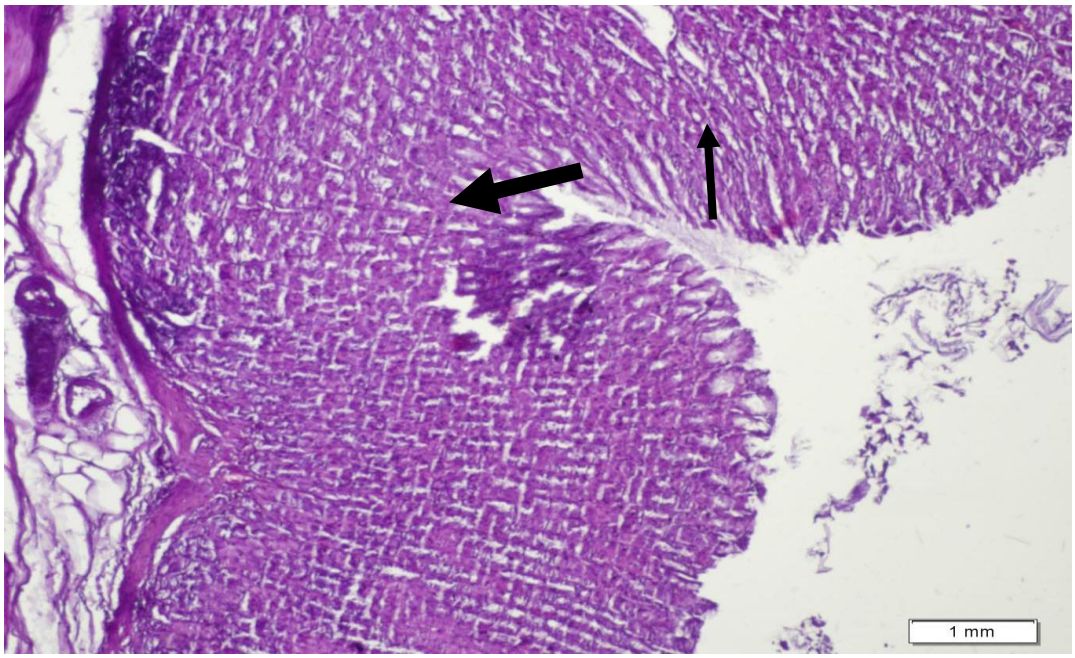

Image 4:- Histological section in stomach (group II- Pantoprazole , 3 mg/kg , x200 , H&E stain).