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Research Article

Gastroprotective Efficacy of Folic Acid and Omeprazole in Indomethacin-Induced Gastropathy in Rats

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ABSTRACT

Gastric and intestinal mucosal damage is the commonest adverse effect of NSAIDs. Their use is associated with a significant risk of hemorrhage, erosions, and perforation of both gastric and intestinal ulcers. NSAID-induced ulcers can be prevented largely through co-administration of a proton pump inhibitor to block acid secretion in the stomach. Also there is a role for folic acid in the attenuation of indomethacin induced gastric ulceration. Study the effect of Folic acid and its association with the antisecretory drug Omeprazole (Proton pump inhibitor) for their abilities to protect gastric mucosa against the indomethacin-induced gastric ulcer. The experiments had been done on 10 white wistar rats for each group. Gastric ulcer was induced by administration of indomethacin (20 mg/kg i.p.). Folic acid (2 mg/kg, orally) has been given for the first group, while Omeprazole (20 mg/rat, orally) has been given for the second group and Folic acid (2 mg/kg, orally) with Omeprazole (10 mg/rat, orally) has been given for the third group as a repeated administration (once daily for 7 days). The gastric ulcers in stomach's rat were examined histological and macroscopical .The ulcer Index and protective Index were calculated. Then the glycoproteines of stomach's mucus gel was measured by spectrophotometer. The combination-treated group (Folic acid and Omeprazole) gave significant increase in the amount of gastric mucosa as compared to Indomethacin group and in comparing to each drug alone the protective Index was increased while ulcer Index retreat. It could be concluded that the combination-treated groups afford a good gastro-protective potential against the gastric ulceration induced by indomethacin better than each drug alone. The antioxidant effects of folic acid and omeprazole are involved and ameliorating the oxidative stress induced by indomethacin in the gastric mucosa.

Keywords: Ulcer, Omeprazole, Folic acid.

INTRODUCTION

Peptic ulcer occurs when there is an imbalance between the damaging effects of gastric acid and pepsin, and the defense mechanisms, which protect the gastric and duodenal mucosa from these substances1. The danger of epithelial arrosion and subsequent ulcer formation exists whenever the protective and reparative mechanisms are weakened and/or the chemical attack by the acid–pepsin mixture is too strong and persists for too long2. The majority of gastric ulcers can be attributed to either H. pylori or NSAID-induced mucosal damage3, particularly in the elderly1. NSAIDs cause serious complications only in a small fraction of NSAID users. Hence, NSAID prophylaxis is advised for those older than 654, cases of cardiac disease5, those with previous history of ulcers or upper GI bleed4,5, and those using anticoagulants and corticosteroids4.

Recent studies suggest that NSAID-induced ulcers in at-risk patients can be prevented largely through co-administration of a proton pump unhibitor6, such as Omeprazole that bind to the H+/K+-ATPase enzyme system (proton pump) of the parietal cell and suppress the secretion of hydrogen ions into the gastric lumen7. This irreversibly inactivates the enzyme causing profound inhibition of acid secretion: a single 20 mg dose reduces gastric acid output by 90% over 24 h. Omeprazole is degraded at low pH and must be given in enteric-coated granules1. 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. Clinical studies have shown that PPIs reduce the risk of bleeding from an ulcer caused by aspirin and other NSAIDs7.

Folic acid (or folate), is a water-soluble vitamin8. Folic acid is used to prevent or cure deficiency of folate which is due either to a decreased supply or to an increased requirement. Deficiency of folic acid leads to a megaloblastic anaemia because it is necessary for the production of purines and pyrimidines, which are essential precursors of deoxyribonucleic acid (DNA)24. Folate modulates a number of disorders as a result of its anti-apoptotic and anti-oxidative properties9. The gastroprotective activity of folic acid supplementation at the basal requirement supplemental dose of 2 mg/kg diet against the lipid peroxidative activity of indomethacin was mentioned10.

MATERIALS AND METHODS

Animals: Fifty male albino rats of the Wistar strain weighing between 180-250 g were used for this study. The animals were separated randomly into ten cages of five rats each where they were kept for four weeks before the start

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Table 1: Effect of folic acid, omeprazole and combination between them on ulcer number, ulcer acuity, ulcer index, and preventive index in indomethacin- (INDO-; 20 mg/kg, i.p.) induced gastric injury.

	Number of animals	Ulcer number	ulcer acuity	percentage of animals with ulcers / 10	Ulcer index	preventive index
CONT	10	0.4 ± 0.266	0.2±0.133	2	2.6	-
INDO	9	9.22±1.128**	3.77±0.547**	10	22.99	0
FOLIC	10	8.6±1.147	3.4±0.4	10	22	4.3
OMEPRAZOLE	7	6.57±0.841	2±0.488*	10	18.57	19.44
OMEPRAZOLE + FOLIC	8	3.125±0.895*	1.25±0.313*	7.5	11.875	48.35

Parametric data were expressed as mean ± S.E.M. P < 0.05. As compared to control (CONT) (**). As compared to INDO (*).

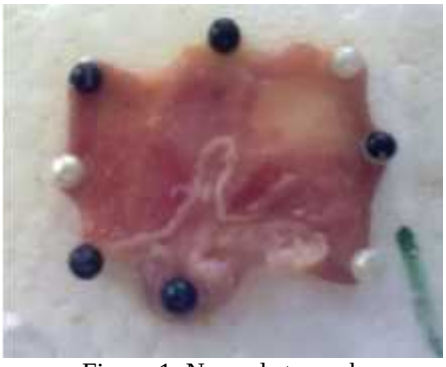

Figure 1: Normal stomach

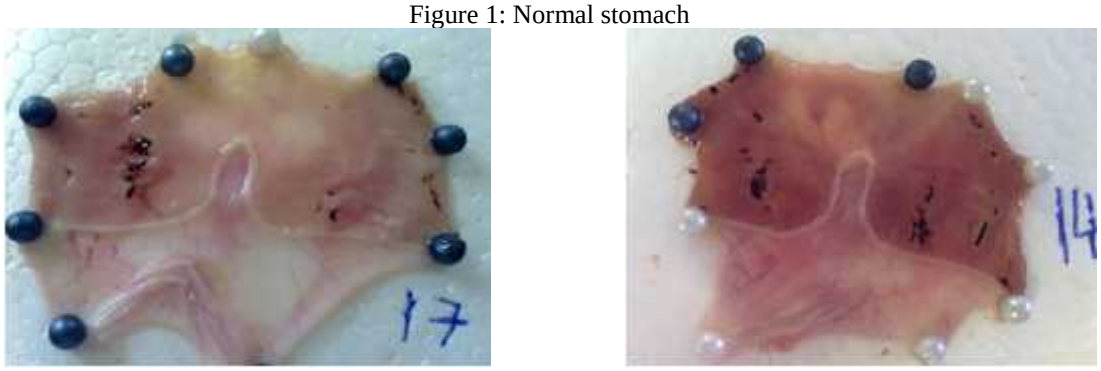

Figure 2: Some large erosions

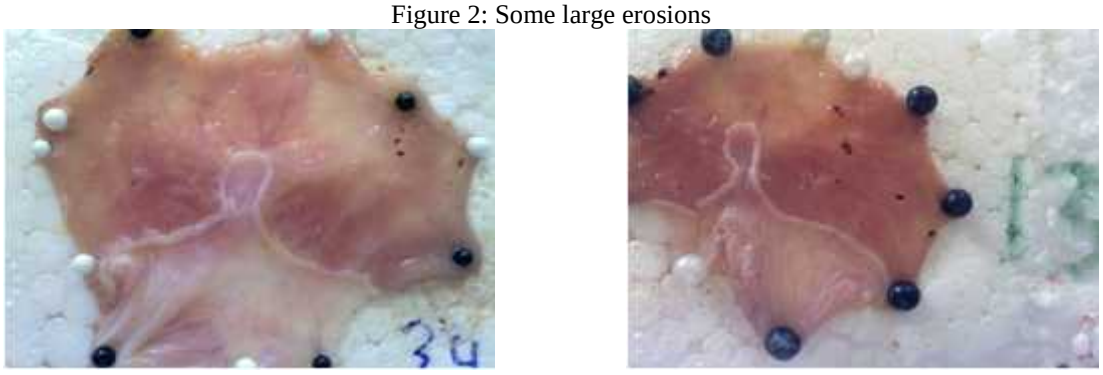

Figure 3: Pin-point petechial hemorrhages

of the experiment. The animals were housed under standard conditions of temperature (23 ± 2°C), humidity (55 ± 15%) and 12 hour light (7.00 am - 7.00 pm). The cages were constantly cleaned in order to prevent the animals from contracting disease. They were fed with standard commercial rat pellets and allowed water ad libitum.

Experimental Design

Table 2: Effect of folic acid, omeprazole as well as their combination on indomethacin-induced (INDO; 20 mg/kg, i.p.) gastric injury histoligically.

Group	NORMAL	INDO	FOLIC	OMEPRAZOLE	OMEPRAZOLE + FOLIC
Grade	0.133 ±0.2	3.11±0.26**	0.395 ± 2.7	0.521 ± 2.286	1.875±0.398*

Values given as mean±SEM. P < 0.05. As compared to control (CONT) (**),As compared to INDO (*).

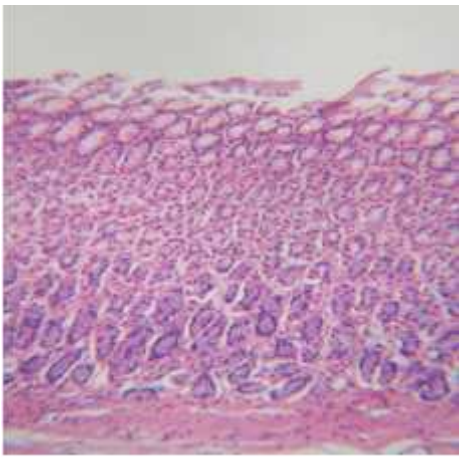

Figure 4: Histological section of gastric mucosa in a rat from Group 1 (NORMAL). Microscopic grade: 0. Note: There is no disruption to the surface of epithelium with neither edema nor leucocytes infiltration of the submucosal layer (H&E stain, 20x magnification).

Grouping: The animals were divided into five groups of ten rats each.

- Group One (NORMAL): Animals were treated with normal saline for seven days. They were called the control group.
- Group Two (INDO): Animals were treated with normal
- saline for seven days before indomethacin (CSPC Ouyi pharmaceutical.co) administration (20 mg/kg).
- Group Three (FOLIC): Animals were treated with 2 mg/kg of folic acid (Ibn Sina laboratories) for seven days before indomethacin administration (20 mg/kg).
- Group Four (OMEPRAZOLE): Animals were treated with omeprazole (ASIA Pharmaceutical Industries) for seven days (20 mg/rat)11 then indomethacin was administrated (20 mg/kg). This group served as the positive control group.
- Group Five (FOLIC + OMEPRAZOLE): Animals were treated with omeprazole (10 mg/rat) + folic acid (2 mg/kg) for seven days then indomethacin was administrated (20 mg/kg).

The route of administration for folic acid was oral. Folic acid was dissolved in normal saline to give a suspension.
Omeprazole pellets were administrated by feeding tube without dissolving to reach the duodenum in this form and protect them from degradation at low pH in the stomach.
Ulcer Induction12: Animals were singly housed and fasted for 36h in widemesh bottomcages, allowed free access to water except for the last hour before the last dose of the medication. Rats were injected intraperitoneally by indomethacin (20 mg/kg) 1 h after the last dose of the medication and euthanized under deep ether anesthesia 4 h later.

Operative procedure13:After seven days of treatment with the appropriate drug for each group, animals were sacrificed as follow:
The rat was anesthetized and a midline incision was made and the stomach is removed, then the stomach was opened along the greater curvature, stretched moderately by pinning on a cork board, and then the gastric mucosa was examined by naked eye and magnifying lens to:
* count the number of lesions.
*determine the ulcer acuity for each group. Gastric lesions were scored according to the following system:
0: no lesion; 1 : <5 lesions, all <2 mm; 2 : <5 lesions, at least one lesion >2 mm; 3 : 5- 10 lesions, all <2 mm; 4 : 5-10 lesions, at least one lesion >2 mm; 5 : >10 lesions, all <2 mm; 6 : >10 lesions, at least one lesion >2 mm14.
Each lesion was considered as an ulcer to calculate the ulcer index (UI) as described by Robert 15:
UI = a + b + c
a : percentage of animals with ulcers / 10
b : average of acuity score
c : average of number of ulcers per group animals
Then the preventive index (P.I.) of a given drug was calculated by the equation of Hano et al 16.

$$P.I. = \frac{\text{U.I. of IND group - U.I. of pretreated group}}{\text{U.I. of IND group}} \times 100$$

Histopathological techniques: Each stomach was fixed with 10% formalin solution for 24 hours. After fixation, five specimens were taken from each stomach. Then sections were stained with conventional EH stain; at least four sections were prepared from each animal. The stained sections were examined under light microscope and the relevant data were registered.

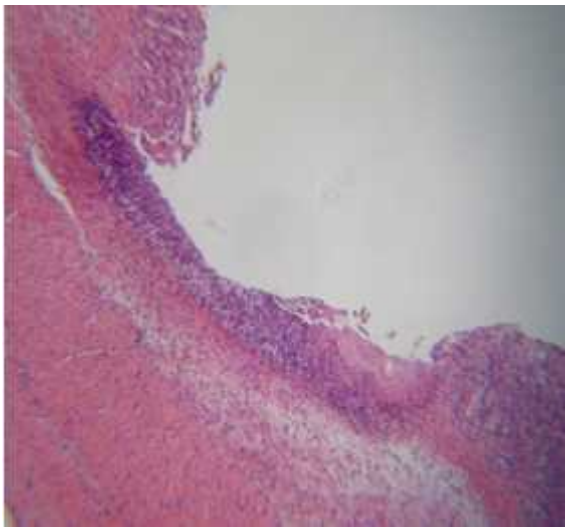

Figure 5: Histological section of gastric mucosa in a rat from Group 2 (INDO). Microscopic grade: 3. Note: There is ulceration till muscularis mucosa with severe inflammation (H&E stain, 20 x magnifications).

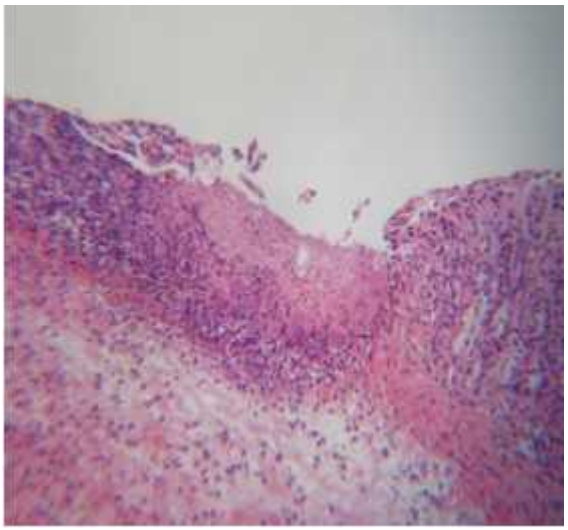

Figure 6: Histological section of gastric mucosa in a rat from Group 3 (FOLIC). Microscopic grade: 3. Note: There is ulceration with inflammation and neutrophiles infiltration (H&E stain, 40 x magnifications).

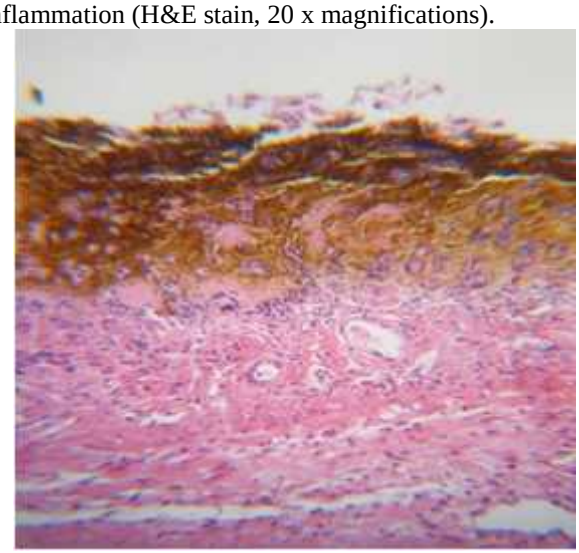

Figure 7: Histological section of gastric mucosa in a rat from Group 4 (OMEPRAZOLE). Microscopic grade: 2. Note: There is surface mucosal abrasion with old haemorrhages and hemosiderin precipitation (H&E stain, 20 x magnifications).

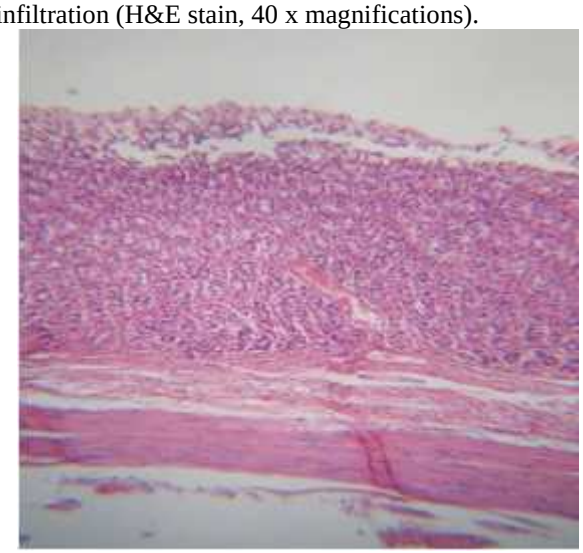

Figure 8: Histological section of gastric mucosa in a rat from Group 5 (FOLIC + OMEPRAZOLE). Microscopic grade: 2. Note: There is mucosal edema and Congestion (H&E stain, 20 x magnifications).

The severity and the degree of mucosal damage were assessed according to modified Sedny scale, so that the following grades were obtained: Grade (0): no mucosal lesions; Grade (1): mucosal edema, congestion, and neutrophils infiltration; Grade (2): surface mucosal erosion. Grade (3): ≤ 2 Gastric ulcers. Grade (4): > 2 Gastric ulcers.

Mucin Content Determination:The gastric mucin was determined according to the method described by Winzler17. Briefly, to diluted samples orcinol (1.6%) and sulphuric acid (60%) were added, vortexed, and boiled for 10min. Mixtures were cooled in ice-cold water to stop the reaction and the absorbance was measured at 425 nm.

STATISTICAL ANALYSIS

All obtained values were expressed as mean + standard error of mean (SEM). By using Mann-Whitney test the proportion of histopathological changes and ulcer acuity in various groups of animals were compared. While the significance of differences between means of ulcers number and mucin content were calculated using the student's t-test. P-values < 0.05 were considered significant. All analysis utilized Prizm4.

RESULTS

Macroscopic study: The macroscopic findings of the opened stomach are shown in Fig. 1. Numerous, tiny, pin-point petechial hemorrhages (figure 3) and large erosions (figure 2) were observed in the indomethacin administered group (INDO, Group 2). Folic acid alone (FOLIC, Group

Table 3: Effect of folic acid, omeprazole as well as their combination on mucin secretion in indomethacin-induced (INDO; 20 mg/kg, i.p.) gastric injury. Values are means ± SEM; comparisons were carried out using Student t-test, P < 0.05. As compared to control (CONT)(**); INDO (*).

Groups	Number of animals	Glycoprotein concentration in mucin SEM ± X
NORMAL	10	8.309 ± 0.346
INDO	9	2.031 ± 0.183**
FOLIC	10	2.536 ± 0.243
OMEPRAZOLE	7	3.655 ± 0.426*
OMEPRAZOLE + FOLIC	8	±0.558 *

Values given as mean±SEM. P < 0.05. As compared to control (CONT) (**), INDO (*).

3) had almost no effects on the stomach, and the coadministration of folic acid with omeprazole inhibited indomethacin-induced ulcer formation (FOLIC + OMEPRAZOLE, Group 5).

Histological evaluation of gastric lesions

Group 1: Most rats in the control group revealed normal squamous gastric epithelium (figure 4). Only two of them showed a mild degree of congestion of blood vessels.

Group 2: Histological observation of indomethacin induced gastric lesions in ulcer control group pre-treated with normal saline only, showed comparatively extensive damage to the gastric mucosa, and oedema and leucocytes infiltration of the submucosal layer (Figure 5). Most rats in indomethacin group experienced the gastric mucosal erosion with the score 3 and 4.

Group 3: Rats that received pretreatment with only folic acid didn't have enough protection of the gastric mucosa as compared to indomethacin group. Six rats in the group of folic acid (2 mg/kg) had ulcers in the stomach and leucocytes infiltration of the submucosal layer.

Group 4: Rats that received pretreatment with omeprazole had comparatively better protection of the gastric mucosa as seen by reduction in ulcer area, reduced or absent submucosal edema and leucocytes infiltration (Figure 2).

Group 5: The combination between folic acid and omeprazole showed cytoprotective effects. Most rats in this group experienced the gastric mucosal erosion with the score 2. Mean gastric erosion scores were demonstrated in Table 2. Pretreatment with Omeprazole and folic acid 1 hour before administration of indomethacin resulted in a decrease in mean gastric erosion score. In addition, there was a statistically significant difference between the combination group and indomethacin group ($p < 0.05$).

Mucin Content Determination: Indomethacin, as shown in Table 3, leveled off mucin concentration in the gastric juice by 75% while folic acid, as well as omeprazole and their combination elevated it (24%, 79%, 95%), respectively, as compared to the indomethacin-treated rats.

DISCUSSION

Experimental studies have demonstrated that nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin are capable of producing injury to gastrointestinal mucosa in experimental animals and humans18. In the present study, injecting indomethacin intraperitoneally (20 mg /kg) induced raise in ulcer acuity, number of ulcers and ulcer index, and decrease mucin content (75%) as compared to control group. Research works on the effect of indomethcin on the gastric mucosa are in agreement with our results. In a previous study, indomethacin decrease gastric mucin concentration by 55.7% and increase ulcer index12. Histological observation showed comparatively extensive damage to the gastric mucosa, and oedema and leucocytes infiltration of the submucosal layer in most of the animals in indomethacin group. There was a statistically significant difference on gastric erosion score between indomethacin group and control group ($p < 0.05$).

The molecular basis for the gastrointestinal toxicity of NSAIDs is widely believed to their inhibitory activity against cyclooxygenase, which causes them to block the production of prostaglandins18. The physiological function of mucosal prostaglandins is cytoprotective, by inhibiting acid secretion, promoting the secretion of mucus and strengthening resistance of the mucosal barrier to back-diffusion of acid from the gastric lumen into the submucosal tissues where it causes damage1. NSAIDs significantly decreased the mucosal prosta-glandin E2 (PGE2) concentration. Charac¬teristically, the damage was observed along the long axis of the stomach and consisted mostly of hemorrhagic lesions, with a few non-hemorrhagic lesions22. Suppression of prostaglandin synthesis is associated with reduction of gastric mucosal blood flow, disturbance of microcirculation, decrease in mucus secretion, lipid peroxidation, and neutrophil activation, which are involved in the pathogenesis of gastrointestinal mucosal disorders18. All NSAIDs, except aspirin, increased gastric motility at ulcerogenic doses, leading to the development of gastric lesions. Gastric hypermotility causes microvascular disturbances, especially at specific sites on mucosal folding, leading to various events including neutrophil-endothelial interaction. In addition, indomethacin caused oxyradical production and lipid peroxidation in the gastric mucosa, probably resulting from the ischemic-reperfusion changes due to rhythmic hypercontraction of the stomach that is mediated by a vagal-cholinergic mechanism22.

Stress, nonsteroidal anti-inflammatory drugs, and H. pylori cause mucosal damage through a number of mechanisms, of which some reactive oxygen species (ROS) such as O2•- and OH• are now considered to be one of the major causative factors for mucosal lesions through oxidative damage. Lipid peroxidation, an important parameter for

OH•-induced oxidative damage of membrane, is increased in gastric lesions caused by ethanol, indomethacin, and water immersion stress. Increased lipid peroxidation, increased protein oxidation, and decreased glutathione level are also evident in restraint cold stress-induced gastric lesions as a result of oxidative damage caused by the significant generation of OH• . Recent studies also indicate that programmed cell death or apoptosis plays a significant role in gastric ulceration. Gastric mucosal lesions caused by stress, indomethacin, ethanol, and H. pylori are also due to increased cell death by apoptosis 19.
The gastroprotective activity of folic acid supplementation at the basal requirement supplemental dose of 2 mg/kg diet against the lipid peroxidative activity of indomethacin was mentioned10. Folate, an important factor in the de novo synthesis of purines, and thymidine, Deoxyribonucleic acid (DNA) stability, and apoptosis, is able to attenuate the development of gastric ulcer. Increase the superoxide dismutase and mucus concentration observed in the folic acid pre-treated group suggests gastroprotective activity of folates, because they are scavengers which mop up and resist free radicals predisposing the stomach to inflammation. Moreover, this is underscored by a decrease in the MDA concentration observed in this group of animals. This could mean that folate inhibits the lipid peroxidative activity of indomethacin 9.
Folic acid (2 mg/kg) was used in previous studies for 21 days. It showed a gastroprotective activity according to its the antioxidative and antisecretory properties 9, 10. While in our study it was used in that dose for 7 days and it didn't show any statistically significant difference between the folic acid group and indomethacin group ($p < 0.05$).
Omeprazole showed, when it was used for 7 days (20 mg/rat), gastroprotective effect against indomethacin-induced ulcer. It decreased ulcer index and increased preventive index. There was important statistically significant difference in decreasing ulcer acuity and increasing mucin content between the omeprazole group and indomethacin group ($p < 0.05$). There is an agreement with previous study showed that pre-treatment with omeprazole decreased gastric lesion formation compared to the indomethacin-induced ulcer group23.
The combination between omeprazole and folic acid was able to attenuate gastric ulceration induced by indomethacin. Ulcer index was low in combination group compared to indomethacin group. The combination resulted in important increase in mucin content and a statistically significant difference when compared to indomethacin group. There was an increase in mucin content (95%) as compared to indomethacin group. Also there were statistically significant differences in ulcer acuity and ulcers number as compared to indomethacin group.
An agreement was found between macroscopic and microscopic results. There was a statistically significant difference between the combination group and indomethacin group ($p < 0.05$). Pretreatment with Omeprazole and folic acid 1 hour before administration of indomethacin resulted in a decrease in mean gastric erosion score.
In addition to the gastroprotective effect of omeprazole through inhibiting gastric acid secretion, a recent study showed antioxidant and antiapoptotic role of omeprazole to block gastric ulcer through scavenging of endogenous hydroxyl radical associated lipid peroxidation and protein oxidation, indicating that its antioxidant role plays a major part in preventing oxidative damage. omeprazole prevents loss of membrane permeability and dysfunction of the cellular proteins, leading to survival of the functionally active cells. Moreover, it offers an antiapoptotic effect by blocking DNA fragmentation during ulceration19.
As a result, the effect of co-administration of folic acid and omeprazole in preventing indomethacin-induced gastric ulcer can be explained through their antioxidant role. So they are able to attenuate oxidative stress induced after indomethacin administration. Indomethacin produces an increase in formation of ROS that catalyze lipid peroxidative and gastric epithelial damage, while folic acid and omeprazole play antioxidant and antisecretory roles, scavenge ROS and reduce their harmful effects thus as a result prevent gastric ulcer formation.

CONCLUSIONS

The combination between folic acid and omeprazole have preventive effect against indomethacin-induced gastric ulcer in rats. Using folic acid (2 mg/kg) for seven days is ineffective in preventing indomethacin-induced gastric ulcer in rats.

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