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RESEARCH ARTICLES / BİLİMSEL ARAŞTIRMALAR

# Comparison of the Protective Effects of Lansoprazole and Omeprazole Against Acetyl Salicylic Acid-Induced Gastric Damage in Rats

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***Comparison of the Protective Effects of Lansoprazole and Omeprazole Against Acetyl Salicylic Acid-Induced Gastric Damage in Rats***

***Summary :*** *Omeprazole and lansoprazole have been reported to be protective against acetylsalicylic acid (ASA) induced gastric mucosal injury due to their proton pump ($K^+/H^+$-ATPase) inhibitor properties. The aim of this study was to investigate the antisecretory, and the antioxidant effects of increasing doses of lansoprazole and also compare them with those of omeprazole against ASA-induced gastric damage in rats. Gastric lesions were induced by administration of ASA (200 mg/kg) to fasted rats. Studies were performed on five groups of animals; control, starvation, ASA, Omeprazole (20, 40, 80 (mol/kg) + ASA and Lansoprazole (1, 5, 10 mg/kg) + ASA groups. Mucosal damage, gastric acidity, as well as lipid peroxidation (LPO), glutathione (GSH) levels and myeloperoxidase (MPO) activity were determined . Both drugs significantly prevented the gastric ulcerogenesis induced by ASA, decreased the ulcer index, and the gastric acidity dose dependently. LPO, and MPO activities, which were increased by ASA, were decreased, and the GSH levels, which were decreased, were increased significantly. According to these findings, as well as the increased acidity, active oxygen species and LPO also play an important role in the pathogenesis of ASA-induced gastric damage. The drugs studied may be protective against this damage due to their antioxidant properties, and also by inhibition of acid secretion.*

***Key Words:*** *Acetylsalicylic acid, gastric mucosal injury, omeprazole, lansoprazole, lipid peroxidation.*

***Sıçanlarda Asetil Salisilik Asit (ASA) ile Oluşturulan Gastrik Hasara Karşı Lansoprazol ve Omeprazolün Koruyucu Etkilerinin Karşılaştırılması***

***Özet :*** *Omeprazolun antisekretuvar ve antioksidan özellikleriyle, asetilsalisilik asit (ASA) ile oluşturulan gastrik gastrik mukozal hasara karşı koruyucu etkileri olduğu bildirilmiştir. Bu çalışmanın amacı lansoprazolun artan dozlarının antisekretuar ve antioksidan etkilerini incelemek ve bu etkileri omeprazol ile karşılaştırmaktır. Gastrik lezyonlar aç bırakılan hayvanlarda ASA (200 mg/kg) uygulaması ile oluşturuldu. Çalışma 5 grupta yapıldı; Kontrol, Açlık, ASA, Omeprazol (20, 40, 80 (mol/kg) + ASA, ve Lansoprazol (1, 5, 10 mg/kg) + ASA. Mukozal hasar, gastrik asit, lipid peroksidasyonu (LPO), glutatyon (GSH) ve myeloperoksidaz (MPO) aktivitesi tayinleri yapıldı. Her iki ilaç da ASA ile oluşturulan gastrik ülseri önemli ölçüde önledi. ASA"ın neden olduğu gastrik asit, LPO ve MPO artışlarını azalttı, ve azalan GSH düzeylerini yükseltti. Bu sonuçlara göre artan asidite kadar reaktif oksijen türevleri ve lipid peroksidasyonu ASA ile oluşturulan gastrik hasarın patogenezinde önemli rol oynamaktadır. İncelenen bu ilaçların gastrik hasara karşı koruyucu etkilerinin onların antioksidan özellikleri ve asit sekresyonunu inhibe edici özellikleri ile ilgili olabileceği görülmektedir.*

***Anahtar kelimeler :*** *Asetilsalisilik asit, gastrik mukozal hasar, omeprazol, lansoprazol ve lipid peroksidasyonu.*

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## INTRODUCTION

Nonsteroidal antiinflammatory drugs (NSAIDs) are known to cause gastrointestinal damage and ulceration, and there is good evidence that acetylsalicylic acid (ASA) exerts direct topical damage[1]. More recently, direct involvement of oxygen-derived free radicals has been implicated in the mechanism of gastrointestinal ulceration [2-5]. Lipid peroxidation mediated by oxygen free radicals is believed to be an important cause of destruction and damage to cell membranes, and attention has been focused on the role of

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reactive oxygen species in mediating the microvascular disturbances that precede the gastric mucosal damage induced by various chemicals, stress, and ischemia-reperfusion, and in the pathogenesis of gastric mucosal injury induced by indomethacin and other NSAIDs [1-6].

In our previous study we demonstrated that the antiulcer drugs, omeprazole and famotidine are protective against ASA induced gastric ulceration due to their antioxidant property as well as their antisecretory effects [7].

Lansoprazole is a relatively new proton pump ($K^+$/$H^+$-ATPase) inhibitor (PPI), and the reports about its antisecretory and antiulcer properties in comparison to omeprazole are controversial[8-11]. Thus, in this study we investigated the protective effect of increasing doses of lansoprazole against ASA-induced damage in comparison with increasing doses of omeprazole.

## 2. Materials and Methods

### Chemicals:

Omeprazole and lansoprazole were donated by İlsan-İltaş Drug Manufacturer and Acetylsalicylic acid by Atabay Drug Manufacturer. All other chemicals were analytical reagent grade.

### Animal treatment

Albino rats of both sexes (150-200 g) were fed a standard diet and water ad libitum. Gastric lesions were induced by administration of ASA to rats, which were fasted for 48hr before the experiments. Studies were performed on five groups of animals: 1 and 2-Control group (C) and Starvation group (S) which were deprived of food for 3 h and 48 h before death, respectively. 3-Acetylsalicylic acid (ASA) group [200mg/kg ASA, orally, suspended in 1% methylcellulose in water], 4- Omeprazole (O) group (20 µmol/kg, 40 µmol/kg or 80 µmol/kg orally, 1h before ASA], 5- Lansoprazole (L) group (1mg/kg, 5mg/kg or 10mg/kg orally 1h before ASA]. Drugs were dissolved in distilled water and were administered by gavage through an intragastric tube.

### Macroscopic analysis:

Two hours after ASA or vehicle (for the control group) administration the animals were killed by decapitation, stomachs were dissected out, cut along the greater curvature, and the mucosae were rinsed with cold normal saline to remove blood contaminant, if any, and the freshly excised stomachs were examined macroscopically for hemorrhagic lesions in the glandular mucosa; The length of each lesion was measured, summed per stomach and used as lesion index[2].

### Examination of gastric acidity:

The pylorus of anesthetized rats was ligated 1 hr after ASA administration. Two hours after pyloric ligation, rats were killed by cervical dislocation and the esophagi were clamped. Samples of gastric juice were collected, centrifuged at 2500g for 10 min, and total acidity was assessed by titration against 0.01N NaOH to pH 7.0 and expressed as microequivalents per 100g body weight per hour[12].

### Tissue myeloperoxidase activity determination:

Tissue associated MPO activity was determined in 0.2 to 0.5 g samples. Tissue samples were homogenized in 10 vol of ice-cold potassium buffer (20mM $K_2HPO_4$, pH 7.4), and then centrifuged at 12,000 rpm for 10 min at 4°C. The pellet was then rehomogenized with an equivalent volume of 50mM $K_2HPO_4$ containing 0.5% (w/v) hexadecyltrimethylammonium bromide. Myeloperoxidase activity was assessed by measuring the $H_2O_2$-dependent oxidation of o-dianizidine 2 HCl. One unit of enzyme activity was defined as the amount of MPO present that caused a change in absorbance of 1.0/ min at 460 nm and 37°C[13].

### Determination of glutathione and lipid peroxide levels:

Tissue samples were homogenized in 10 volumes of ice-cold 10% trihloroacetic acid (TCA) and cen-

trifuged at 3000 rpm for 15 min at 4°C. The supernatant was removed and recentrifuged at 15,000 rpm for 8 min. Glutathione measurements were performed using a modification of the Ellman procedure[14]. Lipid peroxidation was quantified by measuring the formation of thiobarbituric acid reactive substances as described previously[15]. Lipid peroxide levels were expressed in terms of malondialdehyde (MDA) equivalents.

### Statistical analysis:

Statistical analysis was carried out using GraphPad Prism 3.0 (GraphPad Software, San Diego; CA; USA). All data were expressed as means ( SEM. Groups of data were compared with an analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. Values of $p<0.05$ were regarded as significant.

## Results

### Gastric lesions:

Administration of 200mg/kg ASA suspension intragastrically caused hemorrhagic lesions in the mucosa of the glandular stomach, indicating true ulcer formation. The ulcer index was calculated to be 21.0±1.3 mm. Pretreatment of the rats with increasing doses of omeprazole, or lansoprazole prevented gastric ulcerogenesis significantly and decreased the ulcer index dose dependently (Figure 1a).

### Gastric acidity:

In the ASA group, gastric acidity was significantly higher (30±1.95 µEq/100 g body weight/hr) than that of the control group (17.4±0.94 µEq/100 g body weight/hr), and the starvation group (19.9±1.7 µEq/100 g body weight/hr). Omeprazole or lansoprazole administration caused a significant and dose dependent decrease in this parameter (Figure 1b).

The relationship between change in acidity and decrease in the ulcer index values was evaluated for ASA and the increasing doses of PPIs, and a positive correlation was observed ($r=0.822$, $p<0.0001$), implicating the importance of inhibition of acid secretion in the protection against ASA induced damage (Figure 2).

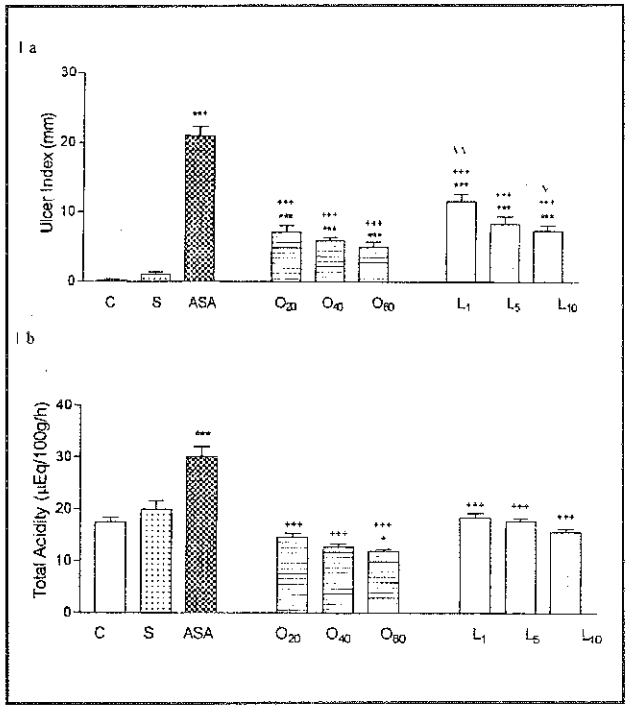


Figure 1: Effect of ASA, and increasing doses of the antiulcer drugs on a) Ulcer index, b) Total acidity. (For each group n=12.) C: Control, S: Starvation, $O_{20}$, $O_{40}$, $O_{80}$: Omeprazole (20 µmol/g, 40 (mol/g, 80 µmol/g) , $L_1$, $L_5$, $L_{10}$: Lansoprazole (1 mg/kg, 5 mg/kg, 10 mg/kg). ***:$p<0.001$, **:$p<0.01$ (in comparison to C group). +++:$p<0.001$, +:$p<0.05$ (in comparison to ASA group). vv:$p<0.01$ $O_{20}$ vs L1, -:$p<0.05$ $O_{80}$ vs L10.

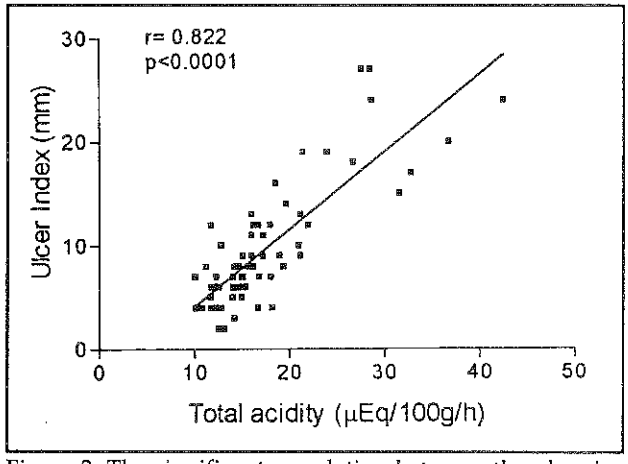


Figure 2: The significant correlation between the ulcer index and total acidity. (The control and starvation data were omitted from the overall data, since these did not have any effect on gastric acidity). The damage caused by ASA increases as the acidity increases, and it is evident that the antiulcer drugs prevent this damage, at least partly, by suppressing the acid secretion.

### Gastric myeloperoxidase (MPO) activity:

Tissue associated MPO activity which is accepted to be an index of neutrophil infiltration was significantly high in the ASA group (63.9±2.0 units/g). Following treatment with omeprazole, or lansoprazole, MPO levels decreased significantly, indicating protection against tissue damage. PPIs seemed to inhibit neutrophil infiltration almost completely at all dose levels, since neither of the MPO activities of these groups were significantly different from the control group (Figure 3a).

The significant correlation (r=0.722, p<0.0001, Figure 4a) between the decrease in MPO activities and the UI, and also between the decrease in acidity and the decrease in MPO activity (r= 0.751, p<0.0001, Figure 4b), (evaluated by using the values for ASA and PPIs) demonstrate that the neutrophil infiltration decreases in parallel to the decrease in the acidity, most probably due to the prevention of the mucosal damage.

### Gastric lipid peroxide (LPO) levels:

Gastric LPO was found to be 21.1±0.69 nmol MDA/g in the control group and 15.9±0.55 nmol MDA/g following 48 hours starvation. ASA administration increased gastric LPO up to 35.9±1.23 nmol MDA/g, whereas omeprazole or lansoprazole pretreatments decreased it significantly (Figure 3b).

The significant correlation (r=0.762, p<0.0001, Figure 5a) between lipid peroxidation and the ulcer index indicate that gastric damage increases with the increase in LPO, and the significant correlation between MPO and LPO values (r=0.821, p<0.0001, Figure 5b) demonstrate that the source of free radicals that cause LPO are mainly the neutrophils.

### Gastric glutathione (GSH) levels:

Forty-eight hour starvation did not cause any significant change in gastric GSH levels when compared to the control group. In the ASA treated group, gastric GSH was found to be significantly decreased. Omeprazole and lansoprazole pretreatments significantly prevented the decrease in GSH levels (Figure 3c).

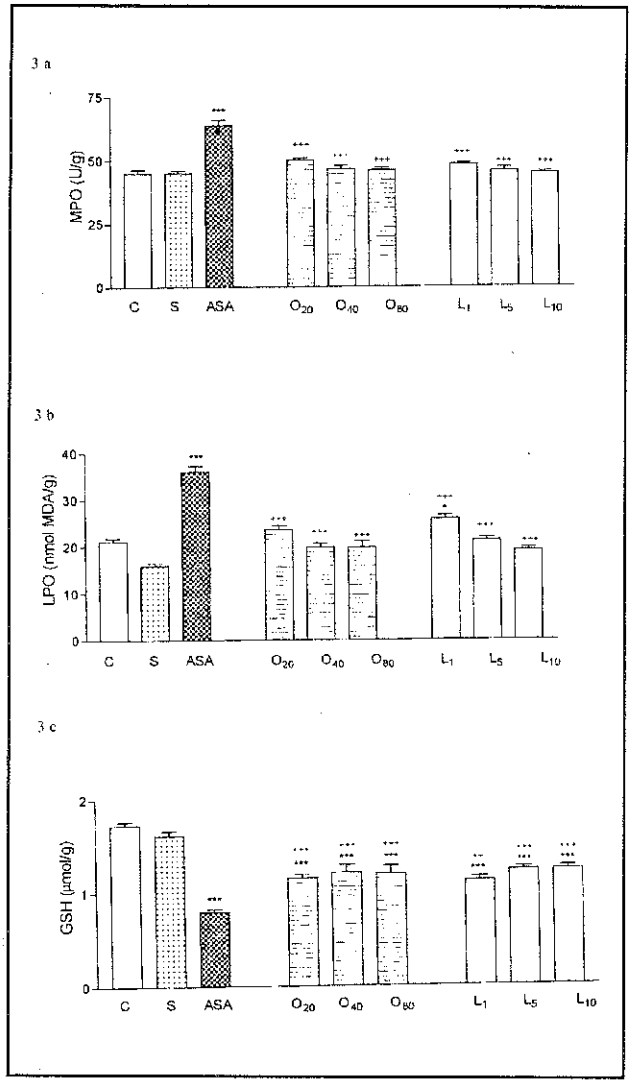


Figure 3. Effect of ASA, and also increasing doses of the antiulcer drugs on a) Myeloperoxidase activity (MPO), b) Lipid peroxidation (LPO), c) Glutathione (GSH). For each group n=12 animals. C Control, S Starvation, $O_{20}$, $O_{40}$, $O_{80}$ Omeprazole (20 µmol/g, 40 µmol/g, 80 µmol/g) , $L_1$, $L_5$, $L_{10}$ Lansoprazole (1 mg/kg, 5 mg/kg, 10 mg/kg). ***p<0.001, *p<0.05 (in comparison to C group). +++:p<0.001, ++:p<0.01, (in comparison to ASA group).

## Discussion

Omeprazole and famotidine have been demonstrated to be protective against gastric injury induced by various agents and stress conditions, and they can cause marked amelioration of gastric damage caused by

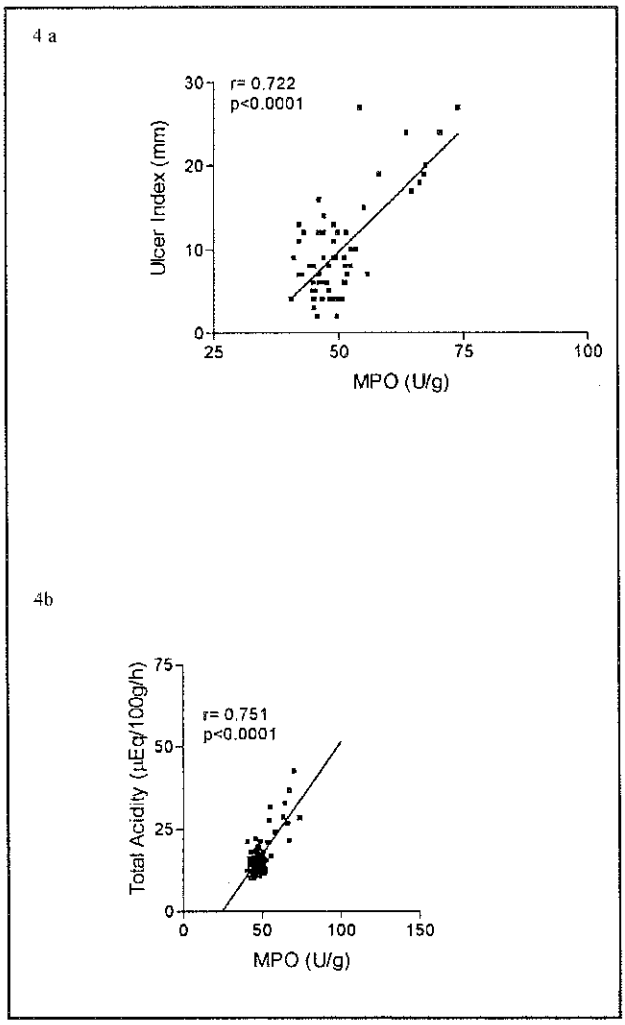


Figure 4. The correlation between increases in a) ulcer index and myeloperoxidase (MPO) activity and b) total acidity and MPO activity. These correlations demonstrate that increase in acidity also increases MPO activity (neutrophil infiltration) which also contributes to gastric damage caused by ASA. The antiulcer drugs may also prevent the damage by preventing neutrophil infiltration as well as by suppressing the acidity, and. that the neutrophil infiltration decreases in parallel to the decrease in the acidity, most probably due to the prevention of the mucosal damage.

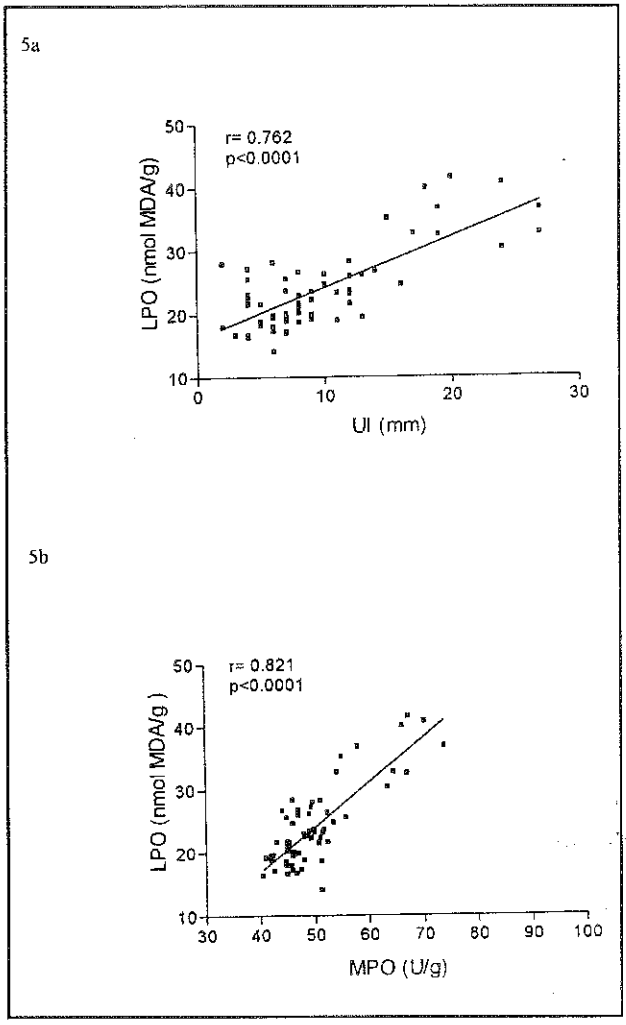


Figure 5: The significant correlation between a) lipid peroxidation (LPO) and ulcer index and b) LPO and myeloperoxidase (MPO) activity. This figure indicates that the gastric damage induced by ASA is an oxidative damage and that it increases with the increase in MPO activity. The antiulcer drugs prevent this oxidative damage in parallel with the increase in dosage.

ASA and other NSAIDs in man and animals[1, 16-19]. The findings of our previous study[7] implicated active oxygen species and lipid peroxidation in the pathogenesis of gastric mucosal injury induced by ASA, and suggested that famotidine and omeprazole are protective against salicylate-induced gastric damage through their antioxidant property, as well as their antisecretory effect. Lansoprazole was also demonstrated to cause a dose-proportional decrease in acid secretion and ASA-induced mucosal damage in healthy volunteers [9], and to prevent water immersion stress or aspirin induced gastric lesions in rats[10]. Thus, in the present study, we aimed to compare the antiulcer properties of omeprazole and lansoprazole and to investigate whether there was any correlation between the antioxidant and the antisecretory effects of these drugs and the dose.

It is well known that salicylates may damage the gas-

trointestinal mucosa, causing lesions ranging from trivial petechiae and superficial erosions to significant and potentially serious deep peptic ulcers[1]. Macroscopic observations of the present study are in agreement with this. In parallel with ulcer formation, the significant increase in lipid peroxidation indicates that lipid peroxidation plays an important part in the pathogenesis of gastric mucosal damage induced by ASA, as reported previously[7].

Pretreatment of the animals with increasing doses of the PPIs decreased ASA-induced gastric damage and inhibited lipid peroxidation significantly, and dose dependently. These observations are in parallel with those of Satoh et al[10] who have reported that lansoprazole, and omeprazole inhibit the ASA-induced gastric lesions in rats dose dependently. The prominent curative and prophylactic effects of the antiulcer drugs on gastric and duodenal ulcers in that study were attributed mainly to the suppression of acid secretion and partly to the protection of the gastrointestinal mucosa against various ulcerative stimuli, although they did not give any further explanation as to the protective mechanisms.

The significant correlation between the degree of inhibition of lipid peroxidation and the decrease in ulcer index indicates that the damage induced by ASA was reduced in parallel with the inhibition of lipid peroxidation. Previous studies, reporting the powerful antioxidant properties of proton pump inhibitors, support our observations[17, 20].

Since the source of oxygen radicals in gastric mucosal injury induced by indomethacin or ASA in rats seems to be the neutrophils, we assessed the role of neutrophils by determining tissue associated MPO activity[1,3]. Myeloperoxidase activity was observed to be significantly high following administration of ASA, and correlation between the MPO activity and LPO levels is another indication that the source of reactive oxygen species is mainly the activated neutrophils. The PPIs inhibited the increase in MPO activity significantly and dose dependently, demonstrating the suppression of neutrophil infiltration by these drugs. Lansoprazole, and omeprazole were demonstrated to have an inhibitory effect on neutrophil function and they were reported to attenuate endothelial cell adhesive interaction of neutrophils induced by extracts of Helicobacter pylori[21,22]. Wandall has also reported that omeprazole may inhibit the neutrophil function under in vitro conditions[23].

The significant correlation between the inhibition of MPO activity and the decrease in ulcer index suggests that prevention of neutrophil infiltration by the antiulcer drugs help reduce the ASA-induced damage. We also observed a significant correlation between the inhibition of acid secretion and MPO activity, indicating that increased acidity may be increasing the mucosal damage, thus facilitating neutrophil infiltration, and contributing to the damage induced by ASA. This observation is supported by the report that ASA and other NSAIDs cause more severe injury in the presence of high levels of intraluminal acid, as will be discussed later[18].

Recently much attention has been focused on neutrophil-derived factors in mediating the gastrointestinal ulceration and inflammation related to the use of NSAIDs[24], since damage to vascular endothelium was reported to be similar to what had been observed in models of ischemia-reperfusion injury, where neutrophils have been reported to play a critical role as mediators of endothelial damage[25]. In studies where the pathogenesis of experimental NSAID gastropathy was investigated, it was observed that administration of NSAIDs to rats resulted in an increase in the number of neutrophils adhering to vascular endothelium in the gastric and mesenteric microcirculation and that the endothelial damage was completely prevented by prior depletion of circulating neutrophils[1].

Glutathione is an important constituent of intracellular protective mechanisms against various noxious stimuli, including oxidative stress[24,26]. In this study decrease in GSH following administration of ASA was accompanied by an increase in lipid peroxides. Omeprazole and lansoprazole inhibited GSH depletion in proportion with their efficacy as antioxidants. Thus, it may be proposed that the antiulcer

drugs may be preserving the tissue GSH levels by preventing lipid peroxidation.

The ability of ASA to cause epithelial damage may be related in part to its accumulation in these cells because of the phenomenon of ion trapping[1,17]. The consequent topical toxicity of salicylates is well recognized and results in impaired barrier function, reduced mucus and bicarbonate secretion and capillary injury. Thus, some have claimed that ASA or some other NSAIDs cause more severe injury in the presence of high levels of intraluminal acid[18]. On the other hand, at the level of intragastric pH achieved with the proton pump inhibitors ASA ionization is virtually complete, and in this form passive absorption of ASA into the gastric mucosa does not occur and mucosal damage is significantly reduced[27]. Thus, the ulcer healing properties of proton pump inhibitors were claimed to be due mainly to the inhibition of gastric acid secretion[10]. Since it has been stated that gastric acidity is crucial in the genesis of aspirin related gastroduodenal injury, increasing doses of lansoprazole, and omeprazole may improve gastric tolerance to and affording protection against ASA induced ulcerogenesis most probably by their antisecretory effect in addition to their antioxidant properties.

In the present study, the strong and significant correlation between the inhibition of acidity by increasing doses of the PPIs and the decrease in ulcer index is in support of this view. It may also be suggested that in the present study omeprazole afforded better protection against ASA-induced damage than lansoprazole, because it was more efficient than lansoprazole in inhibiting the acid secretion. However, the difference between the two drugs was not significant at different dose levels.

In conclusion, findings of the present study indicate that the antiulcer drugs omeprazole and lansoprazole possess a protective effect against acute gastric mucosal injury induced by ASA, and that this protection is dose-dependent. They may afford protection by their direct antioxidant properties, prevent neutrophil induced oxidative damage and also inhibition of acid secretion, since results of the present study implicate the increased acidity as one of the main sources of damage caused by ASA.

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