Effects of Combined Treatment with Aspirin and Diclofenac or Indomethacin on the Gastric Mucosa of the Rat (Reduced Damage by Proton Pump Inhibitors)

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Abstract

Objectives: To investigate the gastric mucosal injury caused by the combined treatment of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) and to identify the optimum methods to avoid such injury.

Methods: Sixty albino Wistar rats of 200-250gm were used in this study. The animals were divided into 8 groups. Group I served as control and received the vehicle of the used drugs (aspirin, diclofenac and indomethacin). Groups II, III, and IV received single daily dose of aspirin (4mg/kg body weight), diclofenac (2mg/kg. body weight) and indomethacin (2mg/kg body weight) respectively. Group V received aspirin and diclofenac and Group VI received aspirin and indomethacin as above. Group VII and VIII received omeprazole (2mg/kg body weight) one hour befor ingestion of aspirin and diclofenac or aspirin and indomethacin as above. At the end of treatment, lesions in the stomach were evaluated macroscopically and microscopically.

Results: Macroscopic analysis showed that treatment with aspirin, diclofenac and indomethacin separately induced multiple gastric mucosal lesions which were larger and deeper following the combined treatment of aspirin and either diclofenac or indomethacin. Microscopically the lesions include increased mucous production, oedema, congestion, necrosis and hemorrhage of the fundic mucosa. After the administration of omeprazole (proton pump inhibitor) most of the mucosal lesions show evidence of partial healing.

Conclusion: Combined treatment with aspirin and diclofenac or indomethacin produced larger and deeper gastric fundic mucosal lesion than aspirin treatment alone. Omeprazole ingestion added to the above drugs significantly healed lesions compared to the control group by 75% and 70% (p=0.05).

Keywords: Aspirin, Diclofenac, Indomethacin, Gastric Ulcer Protection.

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Introduction

Nonsteriodal anti-inflammatory drugs (NSAIDs) are of significant clinical value, accounting for nearly 5% of all prescribed medications [1]. Aspirin was synthesized as the first (NSAID) a century ago, and since then several types of (NSAID) have been developed.

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Nonetheless (NSAID) use is often associated with gastrointestinal complications [2] with approximately 15 to 30% of long-term users experiencing gastrointestinal ulcers and bleeding [3,4,5,6]. In the united states alone, approximately 16,500 people per year die as a result of these complications [7]. The anti-inflammatory action of (NSAIDs) is mediated through their inhibitory effect of cyclooxygenase (COX) activity. COX is an enzyme essential for the synthesis of prostaglandins (PGs). The inhibitaion of COX was believed to be the sole explanation for the gastric complications of (NSAIDs), given that PGs exert a strong protective effect on gastric mucosa [8,9]. Ushijima et al. [10] have demonstrated that (NSAIDs) induce in vitro cell death (apoptosis and necrosis) independent of COX inhibition and have suggested that both COX inhibition and NSAID-induced cell death are required to produce gastric lesions in Vivo. There are many uncertainties about the actual state of gastric mucosal lesions due to (NSAIDs) which have been used widely in recent years[11]. The risk of upper gastrointestinal bleeding with aspirin is increased with old age and concomitant medication with NSAIDs [12]. The cardiovascular benefits of low-dose aspirin might be overcome by the risk of gastrointestinal complications, but withdrawal of aspirin therapy can precipitate a cardiovascular event [13]. In old patients long-term (NSAID) therapy is prescribed not only for patients with acute conditions such as trauma but also for the treatment of chronic diseases such as arthropathies, including rheumatoid arthritis and low back pain. In these patients the concomitant use of (NSAID) and aspirin is not uncommon[1].

The main objective of the present study is to describe the gastric mucosal injury caused by the combined administration of aspirin and either diclofenac or indomethacin and to indentify the optimum methods to avoid such injury.

Materials and Methods

Animals: Sixty albino wistar rats weighing 200-250 gm of either gender, obtained from the animal house of the medical school were used for this study. Rats were housed individually in cages, maintained under standard conditions (12 hours light: 12 hour dark cycle) and were fed with standard pellet and water ad libitum.

Drugs: Acetyl salicylic acid (Aspirin, Bayer, Germany) diclofenac (Voltaren, Novartis, Switzerland), omeprazole (epirazole, Eipico, Egypt), indomethacine (indolag, lagap, Switzerland). These drugs and their vekicles were purchased from the corresponding companies.

Animals were randomly divided into 6 groups consisting of 10 rats each. Animals of group I were used as control, and received the vehicle.

Animals of group II were given aspirin at a daily single dose of 4 mg per kg body weight. The drug was dissolved in 1% NaHCO3 and given per os. Animals of group III were given diclofenac at a single daily dose of 2.0 mg per kg body weight per os. Animals of group IV were given indomethacin in a single daily dose of 2mg per kg body weight per os. Animals of group V were given aspirin and diclofenac as above. Animals of group VI were given aspirin and indomethacin as above. Animals of group VII were given the proton pump inhibitor omeprazole at a single daily dose of 2 mg per kg body weight followed after one hour by aspirin and diclofenac as above. Animals of group VIII were given omeprazole as above followed by aspirin and indomethacin as above. Three animals of each group were sacrificed by

cervical dislocation after 3 hours, 3 days and 3 weeks of treatment. One animal of each group was sacrificed two weeks after cessation of treatment. The stomach was taken out and cut open along the greater curvature and the grade of lesions was scored in the glandular part of the stomach with the help of a magnifying glass and a millimeter scale as described by Das and Banerjee[14], according to the following criteria: O=no pathology; 1= a small 1-2 mm ulcer; 2=medium 3-4 mm ulcer; 4= a large 5-6 mm ulcer; 8= a larger > 6mm ulcer. The sum of the total severity scores in each group of rats divided by the number of animals was expressed as the mean ulcer index[14].

Histopathology: After macroscopic evaluation, stomachs were preserved in 10% formaldehyde solution for histopathological studies. In each specimen, paraffin sections of 4 um in thickness were obtained, stained with one of the following methods.

1) Marks and Drysdale (PAS-hematoxylin-aurantia)[15] (triple stain)
2) Alcian blue, PH 2.5-Periodic acid Schiff (AB-PAS)[16]

The above two methods are specific for mucus of the gastric glands. The severity of the hisopathological changes such as changes in mucus production, congestion, oedema, haemorrhage and necrosis were expressed on an arbitrary scale [17] as per the following changes: normal;+ little effect ++; appreciable effect; +++: severe effects; ++++: very severe effects. Ulcer injury was scored by the method described by Takeuchi et al.[18] according to the following criteria: 1= no damage, 2= shallow damage not exceeding 25% of the mucosal depth but not exceeding 75%; 4= deep damage reaching 75% of the mucosal depth. The **ulcer depth index** was calculated by dividing the mean mucosal thickness by mean ulcer depth. The **ulcerated portion** was measured as percentage size of the ulcer in 3 mm of gastric mucosa[19]**statistical analysis**: The results were expressed as mean ± S.E.M and statistical differences between several treatments and their respective control was determined by one-way analysis of variance (ANOVA), followed by Fisher's least significant difference test using the statistical package for social sciences version 14.0 software (SPSS Inc. Chicago, IL, USA) the level of significance was set at $P < 0.05$.

Results

Macroscopic Studies:

Three weeks after treatment, using a magnifying glass, the macroscopic observations showed that aspirin, diclofenac and indomethacine induced multiple gastric mucosal lesions, mostly 3-4mm in size, with bleeding during the observation.

The mean ulcer index for aspirin was 7.4 ± 0.8, for diclofenac 9.6± 1.0 and for indomethacin 8.2 ± 0.77(P=0.001versus control) (fig.1). As a result of a combined treatment of aspirin and diclofenac the ulcer index has increased to 16.6± 1.9 and when aspirin was given with indomethacin the ulcer index reaches 12.5±1.1 (P=0.001 versus control). Adding the proton pump inhibitor omeprazole to the combined treatment with aspirin and diclofenac and aspirin together with indomethacin significantly healed lesions compared to groups V and VI by 75% and 70% (Fig.1) (P=0.05).

Histopathological Studies:

Microscopical data were consistent with macroscopic observation. The erosive defect which appeared macroscopically appeared microscopically with congestion, oedema, necrosis and haemorrhage.

During the first few hours after aspirin treatment, the fundic gastric mucosa showed

excessive production of surface mucous which was associated with congestion and oedema (Fig 2, 3, 4). This was followed after 2-3days by desquamation of surface mucous cells leaving the pit epithelium relatively unaffected (Fig 5).

The more superficial desquamated cells showed evidence of necrosis with deeply stained pyknotic nuclei.

However, some of the superficial cells appear swollen but retained a residual intracellar polarization e.g. with clearly recognizable nuclei and distinctive perinuclear and apical cytoplasmic zones (Fig 6).

After three weeks of aspirin ingestion most of the above changes have decreased or disappeared, although some patchy areas of superficial cells necrosis can still be seen (fig.7). The parietal cells underlying these superficial erosions seem to have remained unultered by aspirin (Fig.8). the treatment with diclofenac or indomethacin produced similar but less extensive changes than with aspirin (Fig. 9). When diclofenac was given together with aspirin and after three days of treatment the fundic mucosa showed extensive mucous production associated with, oedema, congestion and necrosis. The gastric pits disappeared and these changes extended into the basal parts of the glands which showed cystic dilatations filled with secretion (Fig. 10).

After three days of combined treatment of aspirin and indomethacin, the fundic mucosa showed similar but less extensive changes to the above (aspirin and diclofenac), however after three weeks fundic mucosa showed evidence of metaplastic change in which the gastric pits were replaced by stratified squamous epithelium but no mitotic figures or pleomorphism were seen among the metaplastic cells (Fig. 11). Inbetween the patches of squamous metaplasia, the gastric mucosa appeared normal or with early metaplastic change (Fig. 11). Deep to the layers of squamous metaplasia, the gastric glands were formed mostly of parietal cells and the mucous neck cells were rarely seen (Fig. 12). Congestion of the gastric mucosa appeared in the form of dilated blood vessels between the gastri glands (Fig. 12). Two weeks after cessation of aspirin and indomethacin treatment patches of squamous metaplasia showed evidence of pit formation suggestive of the reversible nature of this change (Fig. 13). For animals subjected to PPI treatment in addition to aspirin and diclofenac or indomethacin, regenerative improvements were observed in the mucosal lesions. However some localized oedema and superficial defects were occasionally seen (Fig. 13).

Table 1.Histopathological examination of gastric lesions induced by aspirin and other NSAID

Groups	Size of ulcer in 3mm of gastric mucosa %	Ulcer depth index	Surface mucous	Congestion	Oedema	hge	necrosis
I. Control	-	-	+	-	-	-	-
II. Aspirin	32.5*	2.78*	++	++	++	+	++
III. Diclofenac	39.8*	3.14*	++	++	++	++	++
IV. indomethacin	28.3*	2.33*	++	++	++	+	+
V. II + III	81.5†	1.88†	+++	+++	+++	+++	+++
VI. II + IV	68.2†	1.62†	+++	+++	+++	+++	+++
VII. as in V + PPI	24.5**	2.91**	+	+	+	+	+
VIII. as in VI + PPI	20.8**	3.10**	+	+	+	+	+

hge = hemorrhage, statistical significance. P* < 0.01 versus controls, †P = 0.05 versus Aspirin, P** = 0.05 versus V and VI, -: normal, +:little effect, ++: appreciable effect,+++: severe effect.

Group I Control
Group II Aspirin
Group III diclofenac
Group IV indomethacin
Group V Aspirin + diclof
Group VI Aspirin + indometh
Group VII as In V + PPI
Group VIII as In VI + PPI

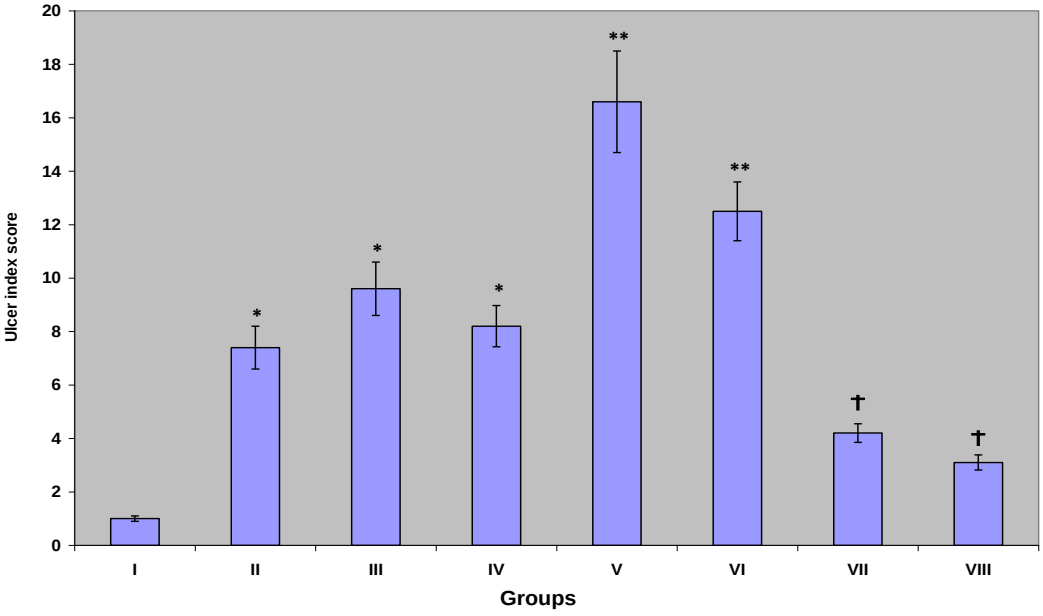

Fig. 1: Effects of Aspirin, diclofenac and indomethacin treatment separately or in combination on gastric mucosa (Ulcer index). Statistical significance: p* = 0.001 versus control P † = 0.05 versus group V and VI. P** = 0.05 versus group II.

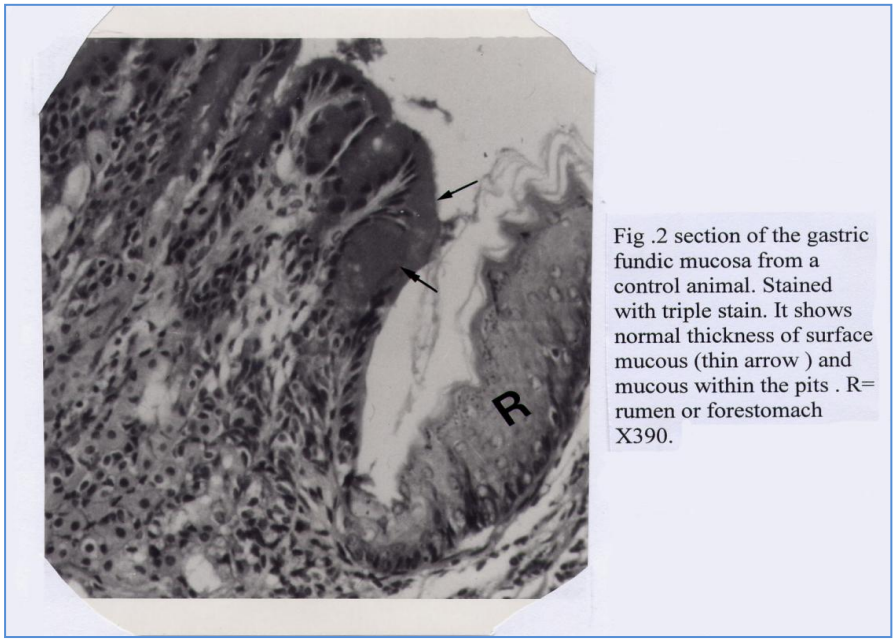

Fig .2 section of the gastric fundic mucosa from a control animal. Stained with triple stain. It shows normal thickness of surface mucous (thin arrow) and mucous within the pits . R= rumen or forestomach X390.

Fig.3 fundic mucosa 3 hours after aspirin ingestion stained by triple stain. It shows excessive production of surface mucous and oedema (thick arrows). The pits (thin arrow) are also distended with mucous. X390

Fig . 4 fundic gastric mucosa 3 hours after aspirin ingestion stained by (AB- PAS). It shows excessive production of mucous by the pit cells (arrow). X280

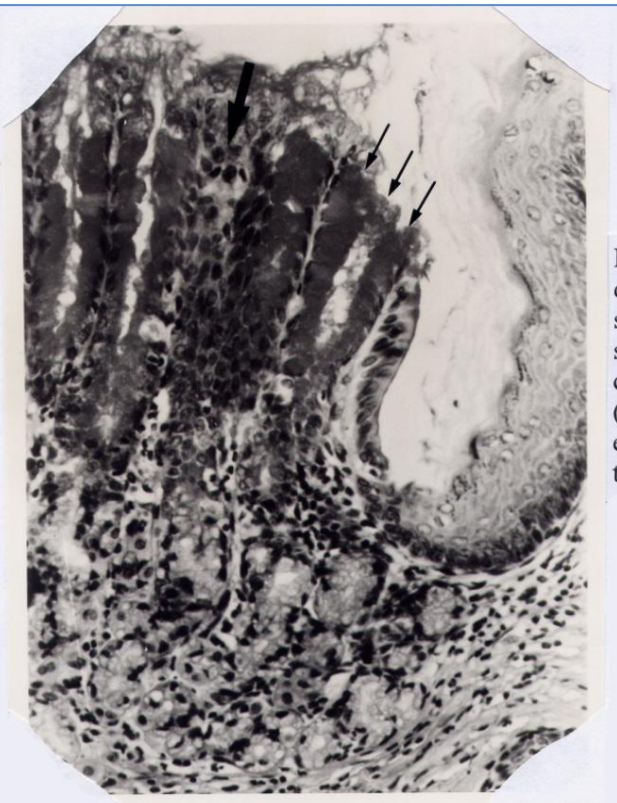

Fig.5 Fundic mucosa 3 days after aspirin ingestion stained by triple stain .It shows desquamation of cells with pyknotic nuclei (thick arrow) as well as erosion of the upper part of the pits (thin arrows). X390

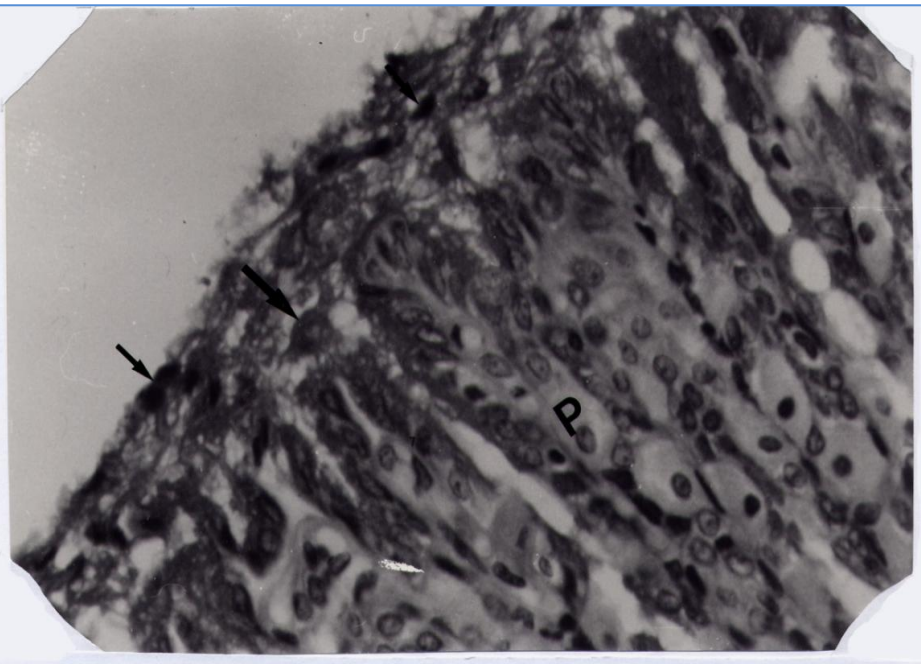

Fig.6 Fundic mucosa 3 days after aspirin ingestion stained by triple stain. It shows desquamated cells with pyknotic nuclei (thin arrow) and some desquamated cells which appear swollen and retained intracellular polarization (thick arrow) and normal parietal cells (p) x 440

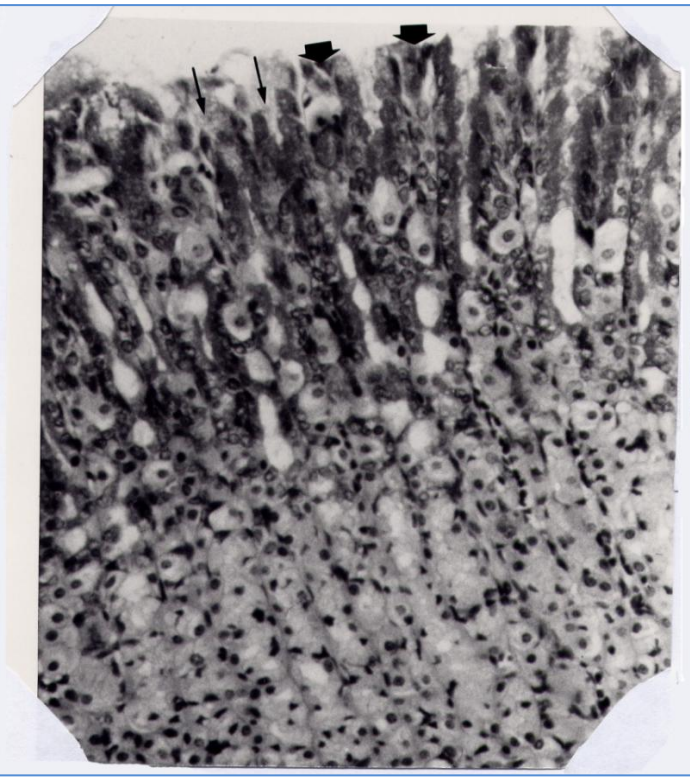

Fig.7 Fundic mucosa 3 weeks after aspirin ingestion stained by triple stain. Most of the pits have regenerated (arrow head) and others still shows necrosis (thin arrow).

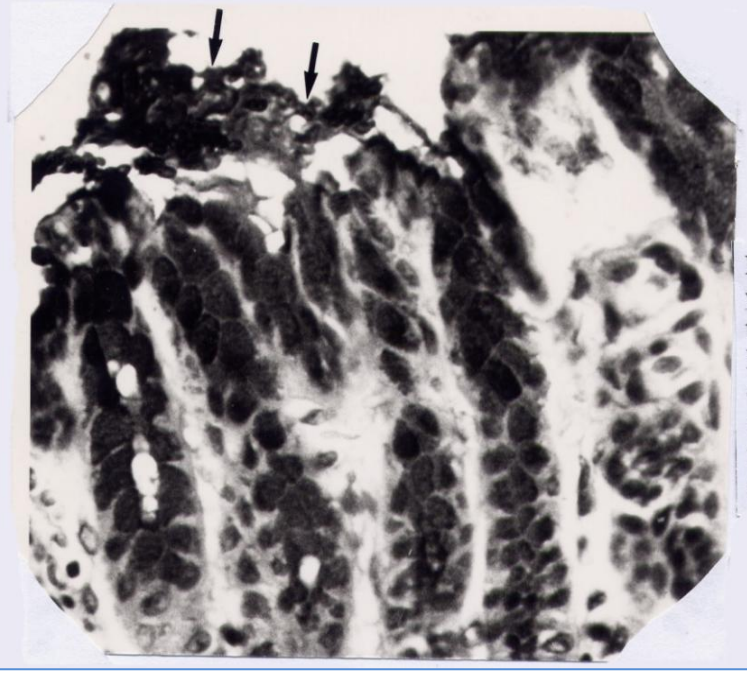

Fig . 8 fundic mucosa 3 weeks after diclofenac treatment staind by (AB-PAS). It show desquamation and necrosis of the superficial parts of the gastric pits (arrows)x280

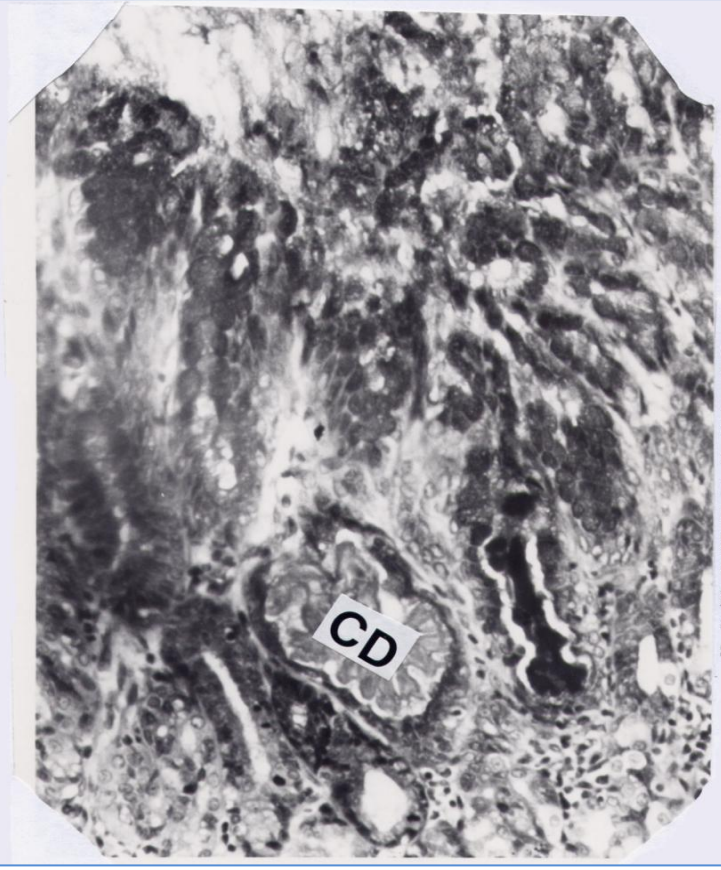

Fig.9 fundic mucosa 3 days after combined treatment with aspirin and diclofenac, stained by triple stain. It shows extensive mucous production, oedema and necrosis. Most of the gastric pits have disappeared and the basal parts of the glands show systic dilataions filled with secretion (CD)x280

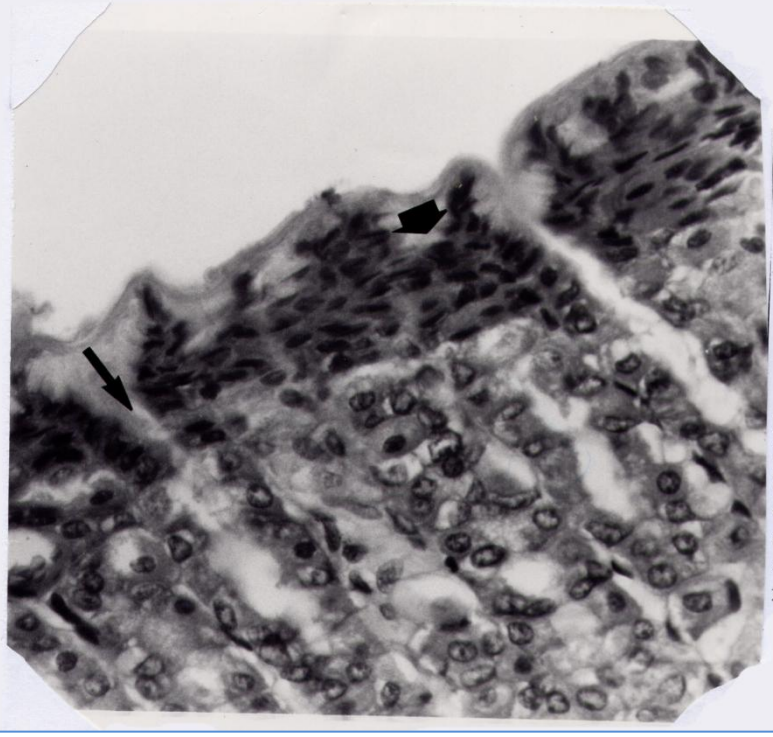

Fig .10 Fundic mucosa 3 weeks after combined treatment with aspirin and indomethacin stained by triple stain. A metaplastic change of the pit cells is suggested by replacement of their cells by stratified squamous epithelium. The process involves fusion of the adjacent walls of the pits which starts at their deep parts (long arrow) and extends more superficially (arrow head) x320

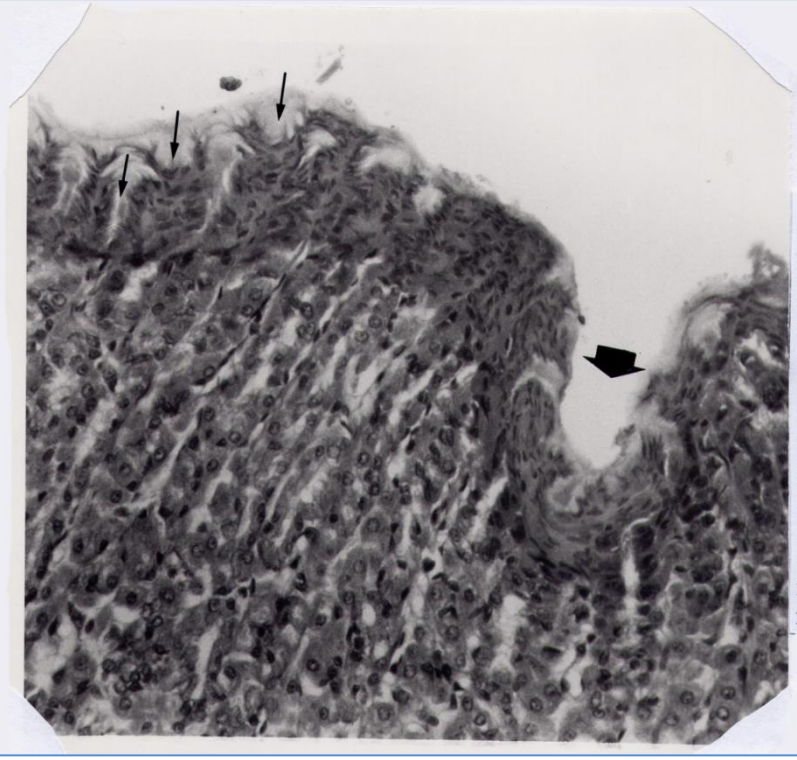

Fig. 11 fundic mucosa two weeks after cessation of aspirin and indomcthacin treatment stained by triple stain. It shows reversible metaplastic changes suggested by the reappearance of the gastric pits within the patch of metaplasia . (arrows) A large erosion can be seen lined by stratified squamous epithelium with few short pits (arrow head) x280

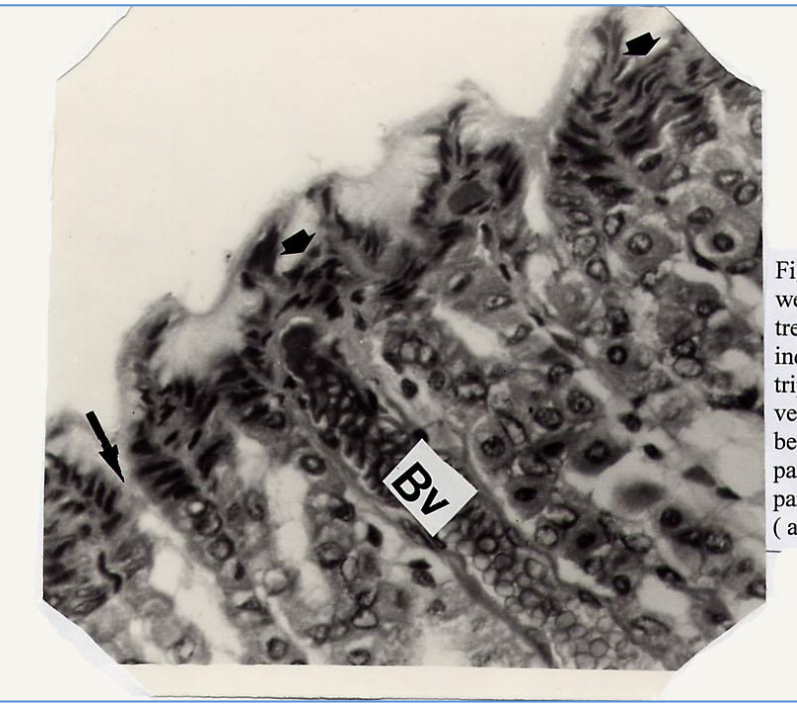

Fig .12 fundic mucosa 3 weeks after combined treatment with aspirin and indomethacin stained by triple stain. A dilated blood vessel (BV) can be seen between the gastric glands- partial fusion in the deep parts of the pits is also seen (arrows) x320

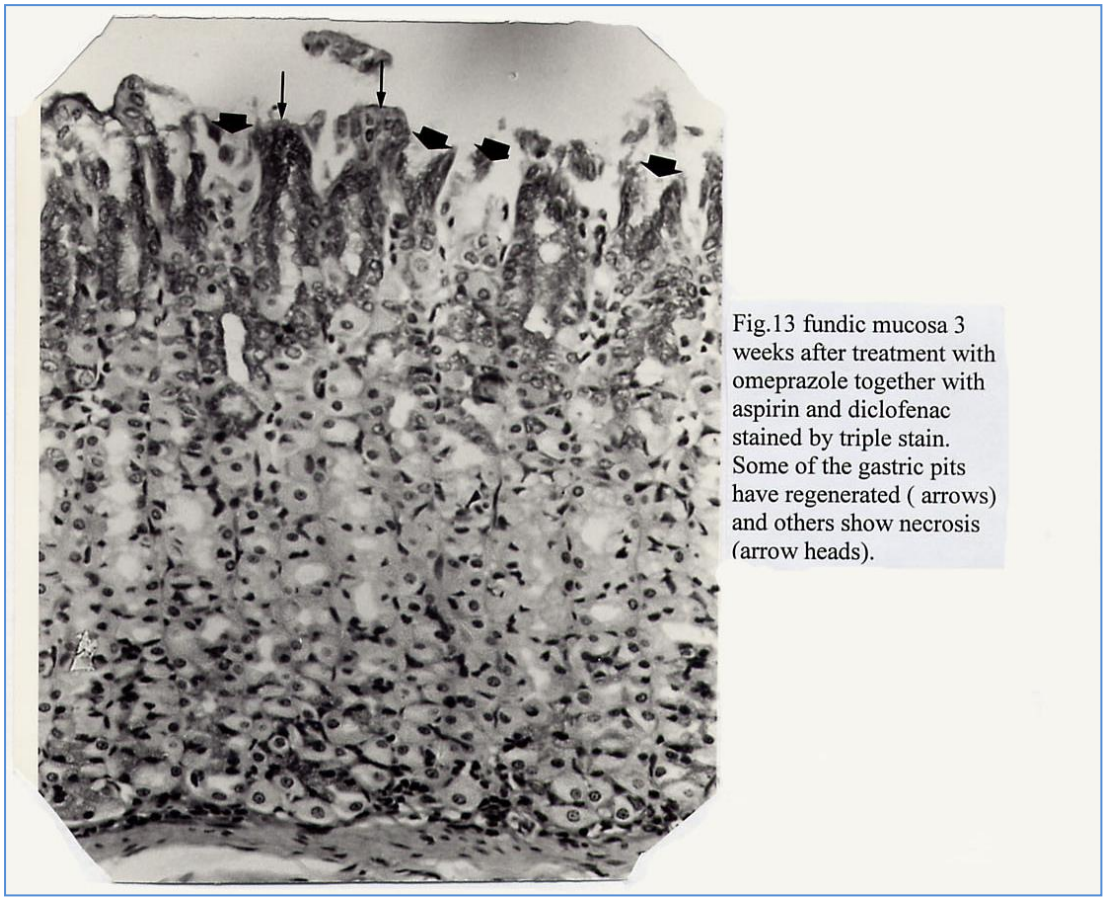

Fig.13 fundic mucosa 3 weeks after treatment with omeprazole together with aspirin and diclofenac stained by triple stain. Some of the gastric pits have regenerated (arrows) and others show necrosis (arrow heads).

Discussion

Oral administration of anti-inflammatory drugs (NSAID) induces gastroduodenal mucosal damage in experimental animals as well as in humans [20].

As the buffered aspirin has been reported to reduce the injury caused by the non-buffered drug [21], aspirin in the present work was dissolved in 1% $NaHCO_3$.

The dose of aspirin in the range we used in this study are widely believed to be harmless to the gastric mucosa. Our study showed, however, that 4mg aspirin/kg body weight caused congestion, oedema, necrosis and haemorrhage; and these effects on the fundic mucosa were much intensified by adding either diclofenac or indomethacin to the aspirin treatment.

Diclofenac is conventionally known to provide a higher risk of upper GI hemorrhage than any other (NSAIDs) [22]therefore, close attention should be paid to its use while a superior analgesic effect is expected [11]. Lichtenberger and his coworkers [23] have proposed that (NSAIDs) disrupt the hydrophobic barrier properties of the gastric mucosal surface, rendering it susceptible to attack by luminal acid. In the present study, it seems that the increased surface mucous production observed during the first few hours following aspirin and other (NSAID) treatment was unable to protect the fundic mucosa against the injurious effects of these drugs.

An important feature of the present study is

that dosing continued for longer periods than in most other studies: Whether the risk of gastric mucosal injury, necrosis and bleeding increased with time or alternatively, whether it decreased by a process of adaptation [24]. Our study showed that the gastric mucosal injury following aspirin treatment is greatest in the first week of ingestion and adaptation occurs with prolonged ingestion. Similar results were obtained when diclofenac or indomethacin was ingested alone. However, the continued ingestion of aspirin together with diclofenac or indomethacin fundic mucosal injury was always observed and evidence of regeneration was seen only after cessation of treatment. These results give support to previous observations that the incidence of peptic ulcers increases when (NSAIDs) which are prostaglandin inhibitors [24] and directly injurious [11], are administered to patients with gastric mucosa affected by various injurious factors like aspirin ingestion or H. Pylori infection. Furthermore, delayed healing of ulcers was reported in patients who took acid-suppressant drugs while continuing to take (NSAIDs) [25]. Recently it has been reported that the prevalence of gastric mucosal lesions reached 58.5% in patients without subjective symptoms, where 10.1% had peptic ulcers[26]. This means that in patients receiving (NSAIDs) subjective symptoms are not a basis for the diagnosis of gastric mucosal lesions, especially peptic ulcers[11]. This supports previous reports that many gastric mucosal lesions due to (NSAIDs) are asymptomatic[27, 28,29].

Although the mechanism responsible for the metaplastic change following indomethacine ingestion is not known, the decrease in ulcer index as compared to diclofenac suggests that the metaplasia may play a protective role against ulceration. The significant decrease in the ulcer index following the ingestion of PPI (omeprazole) indicates that this drug reduces the incidence of gastric mucosal lesions in patients receiving (NSAIDs).

Recently JuSeo et al[30] reported that NSAIDs_induced acute gastric damage increased in a dose-and age-dependent manner which was accompanied by a significant increase in mucosal myeloperoxidase (MPO) levels. The latter is a biochemical indicator of the degree of mucosal neutrophil infiltration.

Experimental and limited clinical studies indicate that aging gastric mucosa has impaired mucosal defenses such as decreased mucus and bicarbonate secretion[31], decreased prostaglandin generation[32] and reduced blood flow[33].

In the present study, the excessive production of surface mucus few hours after aspirin treatment appeared as a first protective mechanism against the injurious effect of NSAIDs.

The limitations of the present study reflect the fact that it is a purely histopathologicalwork. The underlying mechanism such as COX/Prostaglandin pathway and MPO concentration have not been evaluated. Further studies regarding the underlying detailed mechanisms and susceptibility among NSAIDs are planned in the future.

In conclusion, as it is reported that the gastric mucosal lesions are often asymptomatic in patients receiving (NSAIDs) therefore physicians should control pain with (NSAIDs) with a keen recognition that greater awareness of the risk of gastric mucosal lesion and measures for them are essential even if there are no complaints [11].

References

1. 1- Smalley WE, Ray WA, Daugherty JR, and Griffin MR Nonsteroidal anti-inflammatory drugs and the incidence of hospitalization for peptic ulcer disease in elderly persons. Am J Epidemiol, 1995, 141:539-545.
2. Hawley GJ Nonsteroidal anti- inflammatory drug gastropathy. Gastroenterology. 2000, 119:521-535.
3. Barrier CH and HirschowitzBI Controversies in the detection and management of nonsteroidal anti-inflammatory drug – induced side effects of the upper gastrointestinal tract. Arthritis Rheum, 1989, 32:926-932.
4. Fries JF, Miller SR, Spits PW, Williams CA, Hubert HB, and Bloch DA Toward an epidemiology of gastropathy associated with nonsteroidal anti-inflammatory drug use. Gastroenterology, 1989, 96:647-655.
5. Kurata JH and Abbey DE The effect of chronic aspirin use on duodenal and gastric ulcer hospitalizations. J ClinGastroenterol, 1990, 12: 260-266.
6. Gabriel SE, Jaakkinainen L, and Bombardier C Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta- analysis.Ann Intern Med., 1991, 115:787-796.
7. Singh G Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. Am J Med., 1998, 105:31S-38S.
8. Miller TA Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. Am J Physiol, 1983, 245:G601-G623.
9. Vame JR and Botting RM Mechanism of action of anti-inflammatory drugs. Scand J RheumatolSuppl, 1996, 102: 9-21.
10. Hironori U, Ken-inchiiro T, Miho, T, Katus, T, Mina S. Geranylgeranylacetone Protects membranes against Nosteroidal Anti- Inflammatory drugs. Mol. Pharmacol, 2006, 68.1196-1161.
11. Yanhima H, Yamao, J, Fukui H and Takaura,Y. up – to – date information on gastric mucosal lesions from long- term NSAID therapy in orthopedic patients: a study using logistic analysis. J.orthop.Sci., 2007, 12:341-346.
12. Sostres, C, Lanas A: Gastrointestinal effects of aspirin. Nat Rev GastroenterolHepatol, 2011, 7.385-94.
13. James M &Hawkey C: Assessment of NSAID damage in the human gastrointestinal tract.Br.J..clin. Pharmacol, 2003, 56.146-155.
14. Das D, Banerjee RF: Effect of stress on the antioxidant enzymes and gastric secretion. Mol CellBiochem, 1993, 125:115-125.
15. Marks, I. N. and Drysdale, KM: A modification of Zimmermans Method for defferential staining of the gastric mucosa. Stain Techology, 1957, 32.48-49.
16. Spicer, SS, leppi TJ and Stoward, PJ: suggests for a histochemical terminology of carbohydrate- rich tissue components. J. of Histochemcytochem, 1965, 313:599-603.
17. Shal AH, Khan ZA. Gastroprotective effect of pretreatment with zizyphos sativa fruits against toxic damage in rats. Fitoterapia, 1997, 3:226-334.
18. Takeuchi K, Usehima. K, ohuchi T, okabi S: the role of capsaicin sensitive sensory neurons in healing of HCl – induced mucosal lesions in rats. Gastroenterology, 1994;104:1524-1532.
19. Shirwalker A, Malini S, Kumar Js: The gastroprotective activity of the ethanal extract of Agevatumconyzoides. J Ethanopharmacol, 2003, 86:117-121.
20. Ligumsky M, Sesteiri M, Karmeli F, Zimmerman J: Rectal administration of nonsteroidal anti-inflammatory drugs- Effect on rat gastric ulcerogenicity and prostaglandin E2 synthesis. Gastroenterology, 1990, 98:1245-1249.
21. Hawthorne AB, Mahida YR, Cole, AT, Hakey CJ: Aspirin – induced gastric mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. Br. J. clin.pharmacy, 1991,

32:77-83.
22. Sakamoto C, Sugano K, Ota S, Takahashi S: case – contral study on the association of upper gastrointestinal bleeding and NSAIDs in Japan. Eur. J clinpharmacol 2006; 62: 765-72.
23. Lichtenberger. LM, Wang ZM, Romero JJ, Ulloa C, Perez JC, Giraud MN, and Barreto JC Non–steroidal anti- inflammatory drugs (NSAIDs) associate with zwitterionic phospholipids: insight into the mechanism and reversal of NSAID- induced gastrointestinao injury. Nat Med (1995) 1:154-158.
24. Prichard P, kitchingman G, Walt R, Daneshmend T, Hawkey C. Human gstric mucosal bleeding induced by low dose aspirin but not warfarin. BMJ. 1989; 298: 493-6.
25. Scholen RT, Vender RJ. Mechanism of nonsteroidal anti- inflammatory drug – induced gastric damage. Am J Med 1989; 84: 449-458.
26. Lancaster MJ, Jackson DA..Rantidine in the treatment of NSAID associated gastric and duodenal ulcers. Gut. 1991, 32:252-5.
27. Shiokawa Y, Nobenage T, Ogawa A: Epidemiological study on upper digestive injuries by NSAIDs. J Jpn Rheum Assoc 1991; 31:96-111
28. Armstrong CP, Blower AL. Non- steroid anti- inflammatory drugs and life threatening complications of peptic. Gut 1987;28:527-32.
29. Singh G, Ramey DR, Morfeld D, Shi H, Fries JF: Gastrointestinal tract complications of nonsteroid anti – Inflammatory drug treatment in rheumatoid arthritis: a prospective observational cohort study. Arch Interm Med 1996;156:1530-6
30. Pyoungjuseo, Nayoungkim, Joo-Hyonkim, Byoung Hwan Lee, Hyeseung Lee, Hyun Chang, Hyun chee and sung song: Comparson of indomethacinm Diclofenac and Aspirin-induced Gastric damage according to Age in Rats. Gut Liver, 2012 Apr 6(2): 210-7 EPub 2012 Apr 1.
31. Kang JM, Kim N, Kim JH:Effect of aging on gastric mucosal defense mechanisms: ROS, apoptosis, Angiogenisis, and sensory neurons. Am J physiolGastrointest Liver physiol., 2010, 299: G 1147_G 11153 [PubMed]
32. Cryer B, Redfer JS, GoldSchmeidt M, Lee E: Effect of aging on gastric and duodenal mucosal prostaglandin concentrations in humans. Gastroenterology; 1992, 102 (4 Pt.1): 1118-1123 [PubMed].
33. Goro H, Tachi K, Hisanaga Y et al:Exacerbatory mechanism responsible for water immersion stress-induced gastric lesions in aged rats compared with young rats. ClinExpPharmacol Physio, 2001, 28659-662 [PubMed].

تأثير العلاج بالأسبرين إضافة إلى الدايكلوفيناك أو الاندوميثاسين إلى بطانة المعدة في الجرذ

فرج البسطامي[1]

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الملخص

الهدف: معرفة التأثيرات والنتائج للعلاج بالأسبرين وحده أو بإضافة الدايكلوفيناك أوالاندوميثاسين على تلف بطانة المعدة في الجرذ وإيجاد الوسائل المناسبة لتجنب أو التخفيف من هذا التلف.

الطرق: تم استخدام ستين جرذاً من النوع الأبيض وستربوزنيتراوحبين 200-250 غرام وقسمت الحيوانات إلى 8 مجاميع واستخدمت المجموعة الأولى كمجموعة تحكم ولم تعط أي علاج ، حيث أثبتت دراسات سابقة أن كل الأدوية المستخدمة ليس لها أي تأثير على بطانة المعدة، أما المجموعات الثانية والثالثة والرابعة فقد أعطيت جرعة يومية واحدة من الأسبرين (4 ملغم جرام لكل كيلوغرام من وزن الجسم) والدايكلوفيناك (2 ملغم لكل كيلوغرام) والإندوميثاسين (2 ملغم لكل كيلوغرام) على التوالي، وقد أعطيت المجموعة الخامسة الأسبرين والدايكلوفيناك، والمجموعة السادسة الأسبرين والاندوميثاسين بالجرع نفسها في المجاميع الثانية والثالثة والرابعة. وأعطيت المجموعة السابعة والثامنة الاوميبرازول (2 ملغم لكل كيلوغرام) ساعة قبل إعطائها الأسبرين والدايكلوفيناك أو الأسبرين و الاندوميثاسين حسب الجرعات في المجموعتين الخامسة والسّادسة. تمّ تقييم التلف في أغشية المعدة عن طريق التحليل المجهري (Microscopic) والنظري (Macroscopic) بعد نهاية فترة العلاج لكل مجموعة.

النتائج: أظهر الفحص النظري أن العلاج بالأسبرين أو الدايكلوفيناك أوالاندوميثاسين يؤدي إلى حدوث تلف وتقرحات في بطانة المعدة التي ظهرت بمساحة وعمق أكبر فيما لو أعطي الأسبرين مع الدايكلوفيناك ومع الاندوميثاسين ($P = 0.05$) أما الفحص المجهري؛ فقد أظهر وجود زيادة في افراز المخاط السطحي واحتقان وتلف ونزيف في بطانة قاع المعدة. وبعد إعطاء دواء الاوميبرازول لحيوانات المجموعتين السابعة والثامنة تحقق التئام ملحوظ لقرحة جدار المعدة بالمقارنة مع مجموعات التحكم ($P = 0.001$).

الاستنتاج: إن العلاج بالدايكلوفيناك أوالاندوميثاسين إضافة إلى الاسبرين أدى إلى حدوث تلف وتقرحات في بطانة قاع المعدة أكبر مساحة وعمقاً ممّا لو كان العلاج بالاسبيرين وحده وإضافة الاوميبرازول إلى لأدوية السابقة يؤدي إلى التئام ملحوظ لقرحة جدار المعدة بالمقارنة مع مجموعات التحكم بنسبة تراوح بين 70-75 % ($P=0.001$)

الكلمات الدالة: الاسبيرين، الدايكلوفيناك، الاندوميثاسين، القرحةالمعدية، الاوميبرازول، الوقاية.