تأثيرات مضادات الالتهاب غير الستيرويدية في مخاطية المعدة في الجرذان: مقارنة بين الأدوية المثبطة اللاانتقائية لعمل أنزيم الكوكس2 وتلك المثبطة انتقائياً لعمل هذا الأنزيم

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الملخص

الخلفية: مضادات الالتهابات-غير الستيرويدية كانت ولا تزال من الأدوية الأكثر استعمالاً على نطاق العالم: فهي تستعمل كمضادات التهابية ومضادات آلام وخافضات حرارة. إلاّ أنَّ أثارها الجانبية الضارة، وبصورة خاصة تلك التي تصيب المعدة والأمعاء، جعلت كثيراً من الأطباء حذرين في استعمالها لعلاج حالات التهابات المفاصل المزمنة. على الرغم من أنَّ هذه الأدوية تشكل مجموعة غير متجانسة من المركبات الكيميائية، إلاّ أنَّ آلية عملها واحدة، وهي قابليتها لتثبيط عمل مادة البروستوكلاندين الموجودة في مخاطية المعدة من خلال تثبيط أنزيم السيكلواوكسي جنيز. إن البروستوكلاندين المفرز من مخاطية المعدة يؤدي دوراً حاسماً في حمايته من التأثيرات الضارة للحمض المعدي والببسين.

أظهرت البحوث الحديثة أن هناك نظيرين من أنزيم السيكلواوكسي جنيز: الأول يحفز تصنيع البروستاكلاندين المسؤول عن حماية مخاطية المعدة من التأثير المؤذي للحمض المعدي والببسين، ويطلق على هذا النظير اسم السايكلواوكسي جنيز-1، والثاني يحفز الاستجابة الالتهابية وهو مسؤول عن نشوء الأعراض والعلامات الالتهابية، ويطلق عليه اسم السايكلواوكسي جنيز-2. إن الأدوية المضادة للالتهابات- غير الستيرويدية التي تثبيط عمل كلا الانزيمين تؤدي إلى التخلص من الأعراض الالتهابية، ولكن تؤدي في الوقت نفسه إلى أذية الغشاء المخاطي للمعدة. هذا الأمر دفع الباحثين إلى التفتيش عن مضاد التهاب-غير ستيروئيدي يثبط عمل الكوكس-2 فقط. وبعد سلسلة من البحوث توصلوا إلى هذا الهدف، وظهر جيل من مضادات الالتهابات-غير الستيروئيدية تمتلك هذه الصفات ولكن بدرجات متفاوتة وأعراض جانبية أخرى، وهي بحاجة إلى إعادة تقييم في ضوء المعطيات السريرية.

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هدف هذه الدراسة إلى دراسة واحد من هذه الأدوية وهو السلكوكسب، الذي يعدُّ من أكثرها استعمالاً في الوقت الحاضر، من جهة الآثار الجانبية في مخاطية المعدة ومقارنتها بمضادات الالتهاب-غير الستيروئيدية مثل الأسبرين والأندوسيد.

المواد وطريقة العمل: استخدمنا في هذه الدراسة 40 جرذاً ذكراً من فصيلة (سبرانكو-داولي). قسمت إلى أربعة مجموعات كل مجموعة تضم 10 جرذان. المجموعة الأولى استخدمت كمجموعة سيطرة أولى ولم تعط أي دواء، المجموعة الثانية أعطيت عقار الأسبرين بجرعة 30ملغم/كغم واستخدمت كمجموعة سيطرة ثانية، المجموعة الثالثة أعطيت عقار الاندوميثاسين بجرعة 25 ملغم/كغم، المجموعة الرابعة أعطيت عقار السلكوكسب بجرعة 15ملغم/كغم، كانت مدة العلاج شهراً. في نهاية هذه المدة قمنا بتشريح الجرذان بعد تخديرها وأخذنا المعدة من كل جرذ وفحصناها عيانيا ومجهرياً وثبتنا الموجودات التشريحية النسيجية.

النتائج: تسبب عقار الأسبرين بأضرار شديدة في مخاطية المعدة من حيث سعة انتشارها وعمقها، وقد بلغ معدل مساحة الضرر الذي سببه 9.6 ملم^2، ومعدل عدد التقرحات في ملم^2 كان 6.4 تقرحا. في حين تسبب السليكوكسب بتقرحات اقل شدة من حيث المساحة والعدد، أمَّا الأضرار التي سببها عقار الاندوميثاسين فكانت وسطا بين الاثنين.

الاستنتاج: تسبب عقار السليكوكسب، وهو من مضادات الالتهاب-غير الستيرويدية المثبطة انتقائياً لعمل أنزيم الكوكس 2، بأقل ضرر على مخاطية المعدة عند مقارنته بعقاري الأسبرين والاندوميثاسين. إن الأدوية الجديدة من مضادات الالتهاب-غير الستيروئيدية تسببت أقل قدر من الأذى للمخاطية المعدية مقارنة بالأدوية التقليدية. ولذلك فهي أكثر أماناً للاستخدامات طويلة الأمد، كما هو الحال في التهابات المفاصل المزمنة.

Effects of Non-steroidal Anti-inflammatory Drugs on Gastric Mucosa in Rat: Comparison Between Non-Selective and Selective Cox-2 Inhibitors.

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Abstract

Background:Non-steroidal anti-inflammatory drugs (NSAID) have long been, and still, an essential group of drugs having anti-inflammatory, antipyretic, and analgesic effects. The significant gastro-intestinal toxicity associated with their use in treatment of chronic arthritis remains of great concern in clinical applications. The central pathogenic mechanism in NSAID-induced gastro-duodenal toxicity lies in their ability to inhibit the synthesis of prostaglandins by gastric mucosa through inhibition of cyclo-oxygenase enzyme (Cox). There are two isoforms of Cox enzyme: Cox-1 and Cox-2. The gastro-protective effects of prostaglandins are mediated by Cox-1, while the inflammatory effects are mediated by Cox-2. NSAID lead to inhibition of synthesis of prostaglandins, resulting in toxic effects on gastric mucosa and beneficial anti-inflammatory effects.

Conventional NSAID are non-selective inhibitors of cyclo-oxygenases (i.e., they inhibit both Cox-1 and Cox-2) and thus, they promote the anti-inflammatory response, and inhibit gastric protective effects of prostaglandins. To overcome this problem, drugs that have little or no Cox-1 inhibitory activity have been developed and a new generation of NSAIDs has emerged.

Aim of the study: The aim of the present study is to evaluate the effects of new NSAID, namely Celecoxib on the gastric mucosa, and to compare these effects with those produced by conventional NSAIDs, such as Aspirin and Indomethacin.

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Material and Methods: 40 Spargue-Dawely rats are used in this study. The animals were divided into four subgroups, each group included 10 animals, as follow: group I received no treatment and considered as control, group II received Aspirin, group III received Indomethcine, and group IV received Celecoxib. After one month of treatment the animals were sacrificed and the gastric mucosa in each animal was examined macroscopically and microscopically.

Results:Aspirin caused maximum gastric lesions, both in severity and extent, mainly in the pylorus. Celecoxibe and Indomethacin caused an intermediate degree of gastric damage mainly in the body of the stomach.

Conclusion: Aspirin and indomethacine produced the most sever effect on gastric mucosa, these effects take the form of gastric erosion and ulceration involved especially the pylorus and the body of the stomach respectively.

New generation of NSAIDs, Celecoxib showed less gastric toxicity as compared to traditional generation.

Introduction:

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medications in the world (1). It was estimated that more than 100 million people, worldwide, are taking them on regular basis. These drugs are widely favored because of their analgesic, anti-inflammatory, and antipyretic effects. In addition, they are free from side effects like sedation, mental clouding, nausea, and constipation produced by traditional analgesic drugs such as opioid and related drugs (2). Despite their beneficial role in rheumatic arthritis and related pain, as well as in inflammatory disorders, NSAID therapeutic value has decreased 2 to 3 folds because of the high risk of gastro-intestinal toxicity (3). Although structurally heterogeneous, NSAIDs possess a single common mode of action, which is to block the prostaglandins G/H synthase (cyclooxygenase). This effect of NSAIDs is termed as anti-eicosanoid, anti-prostanoid.

Eicosanoid is the name given to a group of 20-carbon unsaturated fatty acids derived principally from arachidonic acid. This group of agents- which includes prostaglandins, thromboxanes, and leukotriens- are short-lived, extremely potent, and formed in almost every tissue in the body (4). They are involved in most types of inflammation, and on manipulation of their biosynthesis most present anti-inflammatory therapy is based (4). The precursor of all eicosanoid is the arachidonic acid, which is stored mainly in phospholipids of cell membrane. Arachidonic acid is mobilized mainly from cell membrane phospholipids by the action of phospholipase-A2. After mobilization, eicosanoids are further metabolized by cyclooxygenases and lipoxygenases. The cyclooxygenases metabolize the linear structure of eicosanoids into the cyclic structure of the prostaglandins. The lipoxygenases, on the other hand, metabolize ecosanoids into leukotriens and lipoxines.

The anti-inflammatory effect of NSADs is produced by inhibition of the synthesis of prostaglandins G/H synthase (cyclooxygenase). Two isoforms of cyclooxygenase enzyme have been recognized, each encoded by a separate gene and exhibiting a discrete pattern of tissue-specific expression (5). These two isoforms are Cox-1 and Cox-2. Cox-1 is predominantly expressed constitutively and functions as physiologic house-keeping in most tissues, including gastric mucosa, kidneys, and platelets (5). Cox-2, expressed especially in macrophages and synovial

cells, is induced by inflammation and mutagen stimulation (6). It has been proposed that the anti-inflammatory properties of NSAID is mediated through Cox-2 inhibition, while gastrointestinal toxicity is mediated through Cox-1 inhibition (6). Traditional NSAIDs are nonselective Cox inhibitors and differ in their relative inhibitory potency against Cox-1 and Cox-2. The important role of Cox-1 in protecting the GI tract mucosa is supported by the finding that greatest damage to GIT caused by NSAIDs is mainly cause by Cox-1 inhibition (7).

The aim of this study is to evaluate the effects of NSAID-induced gastric lesions and to compare those caused by non-selective Cox inhibitors, such as aspirin and indomethacin, with those produced by selective Cox-2 inhibitors such celecoxib.

Material and Methods:

1. The experimental animals: 40 healthy adult male Sprague-Dewily rats with weight ranging between 200-230gm and aged between 18-20 weeks were obtained from the National Center for Drug Control and Research/Baghdad. The rats were kept in cages each accommodates five animals. The rats were left for one week to acclimatize to the animal house conditions. Meanwhile, they were feeding with standard rodent chew diet and tap water. After this period the animal were randomly divided into four groups each containing 10 animals as following:

Group I received no treatment and served as control.

Group II received Aspirin in a dose of 30mg/kg once daily for one week.

Group III received Indomethacine in a dose of 25mg/kg, for one month.

Group IV received Celecoxib in a dose of 15mg/kg.for one month.

The doses are the standard doses used in rats for assessment of gastric damage induced by NSAID (8). Animals body weight were checked regularly and the dose were calculated according to it.

2. Drugs used in experiment

Aspirin tablets: acetylsalicylic acid obtained as Aspirin 100 each tablet contains acetylsalicylic acid 100mg, Batch No10n. manufactured by the State Company for Drug Industry (SDI), SAMARA-IRAQ.

Indomethacin capsules: Indols derivatives, obtained as Indomin 25 each capsule contains 25mg Indomethacine BP. Batch No.1967. Manufactured by AL-HIKMA's drug company.

Celecoxib capsules: Selective Cox-2 inhibitor, obtained as Celecoxib 200, each capsule contains 200mg. Batch No.011-534620, manufactured by G.D. Searle and CO. USA.

Methods:

1. Preparation of drugs solutions: The drugs were diluted with normal saline to get the accurate dose for each animal according to its body weight. The drugs were administered as liquid solutions through stomach tube.

2.Operative procedure: After one month of treatment with the appropriate drug for each group, animals were sacrificed as follow:

a. The rat was anesthetized and a midline incision was made and the stomach is removed.
b. Then the stomach was opened along the greater curvature, stretched
c. 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 by mm2.
* determine the extent of the lesions by measuring the surface area occupied by the lesions relative to the total surface area of the gastric mucosa.
* study the distribution of ulcers and their grades in various parts of the stomach.

3. Histopathological techniques:

A. Each stomach was fixed with 10% formalin solution for 2days.

B. After fixation, three specimens were taken from each stomach; from the funds us, the body, and the pylorus.

C. The sections were stained with conventional EH stain; at least four sections were prepared from each animal.

D. The stained sections were examined under light microscope and the relevant data were registered.

E. 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): Gastric ulcerations.

4. Statistical analysis

All obtained values were expressed as mean + standard error of mean (SEM). By using Chi-square test the proportion of histopathological

changes in various groups of animals were compared. P-values < 0.05 were considered significant.

Results:

1. Morphometric findings:

The numbers and surface areas of stomach's lesions for each animal were calculated. The values were expressed as mean number and mean surface area; tables 1, 2, 3, and 4. Regarding the distribution of lesions in different parts of the stomach (funds us, body, and pylorus) we found that there is significant differences in distribution of lesions between funds us and body, and funds us and pylorus (P<0.05). The distribution of lesions according to site and severity showed significant differences between body and funds, and funds and pylorus for grade 1. The reverse was seen regarding grade 3. Table 5.

Table 1: Mean number of lesions per mm2 for different groups. Aspirin is considered as second control for comparing the severity of lesions induced by other NSAID.

Group of animal	Lesion number/mm2	% of stomach mucosa involved by lesions	P-value
I	0	0	0
II	6.40 + 0.56	100%	P< 0.001 as compared to normal control
III	5.50 + 0.58	85%	P> 0.05 as compared with aspirin
IV	0. 80+ + 0.24	12.5%	P< 0.05 as compared with aspirin

Table 2:- Mean differences in lesion number/mm2 between different groups.

	Celecoxib	**Indomethsin**	**Aspirin**
Aspirin	5.60 *	0.9	
Indomethasin	4.70		

* P<0.05

Table3:- Mean surface areas of lesions induced by different NSAID for different study groups

Group	Total area of lesion (mm2)	% of the involved gastric mucosa	P-values
I	0	0	/
II	9.10 + 0.61	100%	P< 0.05 as compared with control
III	6.40 + 0.6	70.32%	P>0.05
IV	0.90 + 0.090	9.89%	P<0.05

Table 4:- Mean differences in number of lesions /mm2 produced by different NSAID.

	Celecoxib, 0. 80	Indomethacin 5.50	Aspirin, 6.40
Aspirin, 6.40	5.60*	0.90	
Indomethacin, 5.50	4.70*		

* P<0.05

2. Histopathology findings.

A. Control group.

Macroscopically,the stomach revealed a normal glistening mucosa covered by a thick layer of fluffy adherent mucus.

***Microscopically*.** The funds of the stomach revealed normal squamous non-glandular epithelium. The body revealed normal glandular epithelium with characteristic deep blue oxyntic cells at the base of the glands. The antrum was normal showing the predominance of mucus secreting glands.

B. Aspirin and Indomethacin-treated groups.

Macroscopically. The wall of the stomach appeared stretched and thinner than that in control. Numerous, tiny, pin-point petechial hemorrhages in the body and the pylorus were observed. Much irregularly distributed erosions that are elongated, dark-red and oriented parallel to the longitudinal axis of the stomach were also observed.

***Microscopically*.** The mucosal lesions showed variable depths; most of them have the appearance of superficial hemorrhagic erosions involving

mainly the body and pylorus (figure 1), others are deeper extending throughout the mucosa to involve the sub-mucosa.

There is a heavy infiltration of acute inflammatory cells (neutrophils and macrophages) involving the mucosa and submucosa, as well as mild monocytic infiltrate.

The funds us of the stomach show hyperemia, but is less subjected to erosions compared with the body and pylorus. In few cases the lesion takes the form of overt gastric ulceration that involved the full thickness of the wall of the stomach (figure 2). According to the criteria adopted for assessment of the severity of the lesions the following results were obtained: Tables 5 and 6, and figures 4 ,5, and 6.

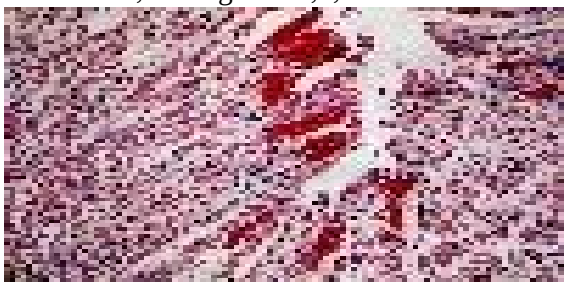

Figure 1: The body of the stomach; Hemorrhagic erosions involving the superficial part of the gastric mucosa. X40

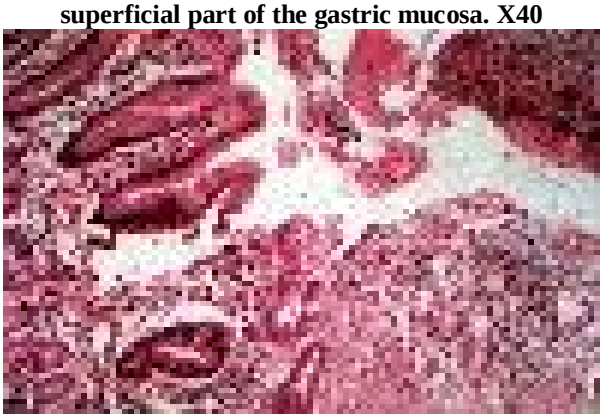

Figure 2: Pylorus; Deep ulceration involving the entire thickness of the gastric wall, X40...

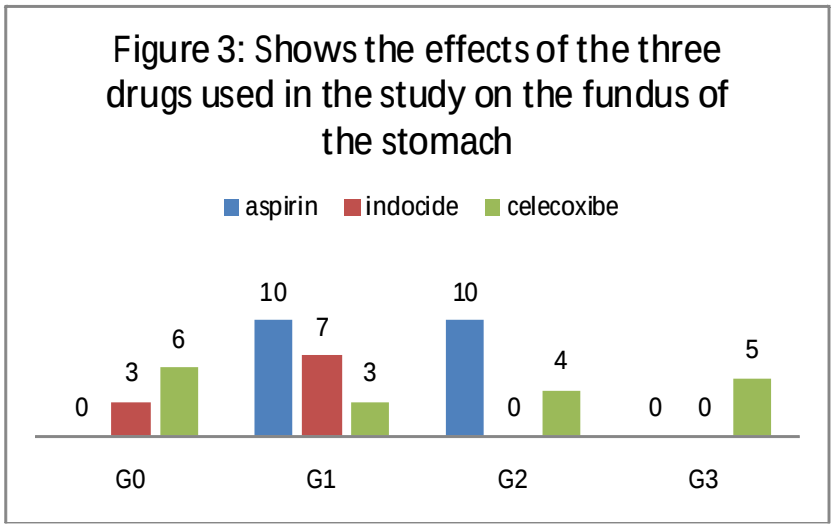
Figure 3: Shows the effects of the three drugs used in the study on the fundus of the stomach
aspirin
indocide
celecoxibe
0
3
6
10
7
3
10
0
4
0
0
5
G0
G1
G2
G3

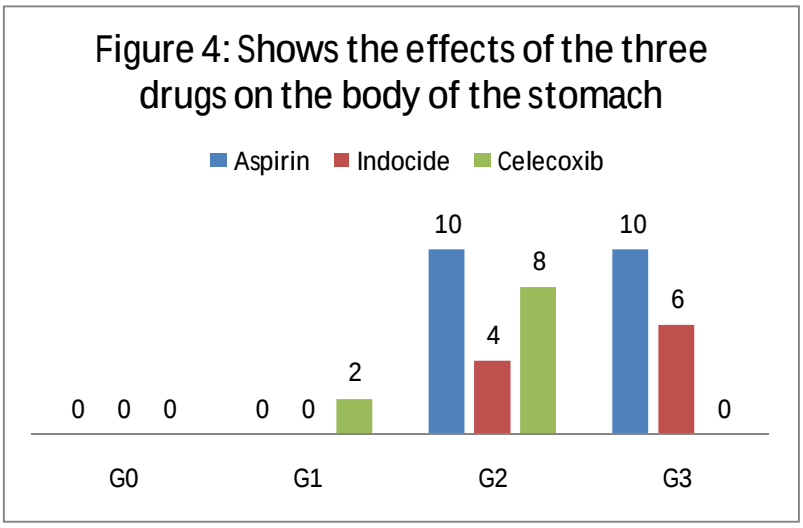
Figure 4: Shows the effects of the three drugs on the body of the stomach
Aspirin
Indocide
Celecoxib
0
0
0
0
0
2
10
4
8
10
6
0
G0
G1
G2
G3

Table 5: Aspirin-induced gastric lesions distributed according to their grades in different parts of the stomach for each case.

Case number	Funds us	Body	Pylorus
1	G1	G2	G3
2	G1	G2	G3
3	G1	G2	G3
4	G1	G2	G3
5	G1	G2	G3
6	G1	G2	G3
7	G1	G2	G3
8	G1	G2	G3
9	G1	G2	G3
10	G1	G2	G3

Table 6:- Indomethacin-induced gastric lesions distributed according to their grades in different parts of the stomach for each case.

Case number	Funds	Body	Pylorus
1	G1	G2	G3
2	G1	G3	G3
3	G1	G2	G2
4	G0	G3	G2
5	G1	G2	G3
6	G0	G3	G2
7	G1	G3	G3
8	G1	G3	G3
9	G0	G2	G2
10	G1	G3	G2

B. Celecoxib -treated groups.

Macroscopically. The number of lesions is less compared to Aspirin and Indomethacine-treated group, table 1. The lesions involved mainly the body and pylorus of the stomach and showed no specific pattern of appearance. Very small and scanty hememorrhagic spots or just hyperemic areas were observed.

Microscopically. There was a mild degree of congestion of blood vessels with a very little inflammatory infiltration. The hyperemic lesions were ficial and hardly extending beyond the superficial lining epithelium to cause frank erosions, this is usually seen in celecoxib-treated animals. There is was erate acute inflammatory cells infiltration, as well as chronic

inflammatory cells. According to Modified Sedny scale the following results were obtained, tables 7.

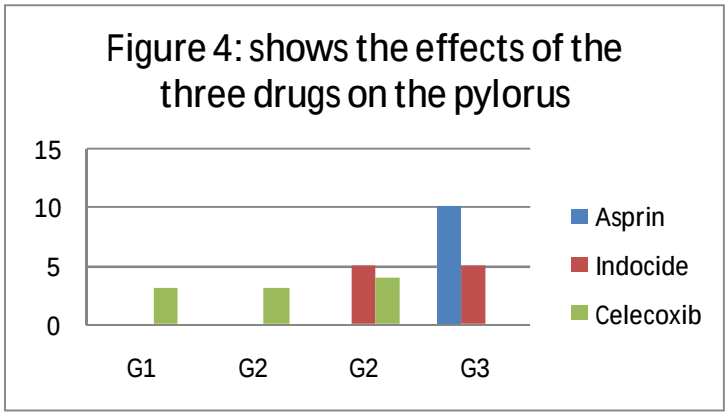

Table 7: Celecoxib-induced gastric lesions distributed according to their grades in different parts of the stomach for each case

Case number	Funds	Body	Pylorus
1	G 1	G2	G2
2	G 0	G1	G2
3	G 1	G2	G0
4	G 0	G1	G0
5	G 0	G2	G0
6	G 0	G2	G2
7	G 0	G2	G2
8	G 0	G2	G1
9	G 1	G2	G1
10	**G 1**	**G2**	**G1**

Discussion:

Protection of gastric mucosa against acid and pepsin:

The factors that protect gastric mucosa against the digestive effect of gastric acid and pepsin play a crucial role in ulcer pathogenesis. Any injurious agent that interfere with or destroys one or more of these protective mechanisms will result in ulcer formation. These protective mechanisms are:

1. The mucus. It is secreted by surface mucous cells and mucous cells present in the neck of the oxyntic gland of the body and funds us, and in the antral and pyloric mucous glands. The mucus secreted by the surface

mucous cells is viscid, insoluble and forms an unstirred layer of gel on the mucosa, with a PH around 7.4 and a thickness more than 1mm (9). The mucus secreted by the glands is thin and helps to protect gastric glands against gastric enzymes.

2. Bicarbonates. The gastric mucosa secretes HCO3- which acts as a buffer system to neutralize gastric acidity. The unstirred layer of mucosal gel and the tight apical junctions between the surface mucosal cells, together with bicarbonates, form the mucosal- HCO3- barrier, which plays the major role in protecting gastric mucosa against gastric secretions and mechanical injuries (9).

3. Gastric mucosal blood flow. Studies on the role of gastric mucosal blood flow had shown that gastric ischemia produced by legation of celiac artery resulted in an immediate fall in blood flow but no gross mucosal lesions (10). When ischemia was followed by reperfusion, gastric erosions develop reaching a maximum at 12hours. When the ulcerations started to heal both gastric mucosal blood flow and prostaglandin E2 levels started to increase (10).

4. Prostaglandins. The normal gastric mucosa is remarkably resistant against the high concentration of HCL and pepsin in the stomach lumen. This is due to the function of mucosal barrier which preserves a high H+ gradient between the stomach lumen (PH 1-2) and the cytosol of mucosal cells (PH 7.4). Prostaglandins improve the gastric mucosal resistance against mechanical, chemical, osmotic, or thermal irritants to the gastric mucosa. The human gastric mucosa produces all known prostaglandins in addition to prostacyclin PGI2. PGE2 is the predominant prostaglandin produced by the gastric mucosa (11). There are different mechanisms by which prostaglandins contribute to the anti-ulcerogenic action:

1. Inhibition of acid and pepsin secretion.
2. Stimulation of mucus and bicarbonate secretion
3. Improve mucosal blood flow
4. Elevation of hydrophobicity of the mucosal epithelial cells.
5. Elevation of the electrical potential difference of the gastric mucosa (12).

Mechanisms of NSAID-induced gastric ulceration.

NSADs produce mucosal injury via local irritating and systemic effect. The later is mediated through cyclooxygenase inhibition. Cycloxygenases are membrane bound glycoproteins which catalyze arachidonic acid into

prostaglandins G2 which have cytoprotactive activity (11). In 1990, it was found that cyclooxygenase activity increases in a variety of cells after exposure to endotoxines, pro-inflammatory cytokines, growth factors, hormones, and tumor promoters (12). This activity requires synthesis of new proteins and is inhibited by corticosteroids. There are two isoforms of cycloxygenases; COX-1 which is constitutively expressed and plays important role in maintenance of normal gastric mucosa and other organs functions, and COX-2 which is the inducible form which is up regulated in areas of inflammation (12).

The severity and extent of gastric lesions produced by NSAIDs.

In general, traditional NSAIDs nonspecifically reduce both cyclooxygenase isoforms, leading to both beneficial antipyretic and anti-inflammatory effects, and unwanted toxic gastrointestinal injury. NSAID that are selective COX-2 inhibitors spare the gastro-protective effects of prostaglandins which are mediated through COX-1 (13).

The result of our study showed that Aspirin and indomethacin produced substantial damage to the gastric mucosa in rats, tables 1, 3, 5, and 6. These effects are both quantitative (number of lesions/mm2) and qualitative (Grade of the lesion). Aspirin 30mg/ Kg/day causes' maximum lesion area (mean 9.1 mm2), as well as the most sever lesions (grade 3) in 100% of cases. When compared to celecoxib 15mg/Kg, which produced the least lesion area (0.9 mm2) and the least sever lesions (grade 1). Research works on the effect of aspirin and NSAIDS on the gastric mucosa are in agreement with our results (14, 15). These findings can be explained by the fact that the active Cox site is a hydrophobic channel with a series of amino acids including seiren 580, arginin 120, and tyrosine 385. Aspirin bind irreversibly to seiren 580 by acetylation, this irreversible binding makes aspirin more harmful to gastric mucosa. Most other NSAIDs satirically and reversibly bind to tyrosine 380 or arginine 120 thus blocking the Cox enzymatic action. (21).

Indomethacin causes ulceration in 70% of cases; these results are in agreement with other studies (16). We found that Celecoxib 15mg/Kg cause ulceration in 10% of cases, this finding is in agreement with Brain and Abramson (18). These wide ranges of differences between aspirin and Indomethacin on one hand, and Celecoxib on the other hand can be attributed to the fact that aspirin and indomethasin are non-selective Cox-1 and Cox-2 inhibitors. Since members of NSAIDs differ in their ability and selectivity in inhibiting Cox-2 enzyme, it follows that their ulcerogenic effects on gastric mucosa are variable. Aspirin and indomethacin are considered as equally selective inhibitors for Cox-1 and Cox-2 enzymes, so they induced the highest percentage of ulcerations (19). Celecoxib is highly selective Cox-2 inhibitors (18), so it causes very

little gastric damage because it preserves the gastro protective effect of Cox-1. The selective Cox-2 inhibitors play an important role in the new management of other diseases such as colorectal cancer (20).

Distribution of ulcers according to grades and locations.

Funds. us Our study has shown that aspirin causes lesions in the funds us in 100% of case, and these lesions are of grade 1 in 100% of cases. Indomethacin produced fundic lesions in %70 of cases, and these are of grade 1 in 100% of the cases. Celecoxib affects the funds in 40% of the cases, and these are of grade 1 in 100% of cases. The explanation for this reduced liability of the funds to the injurious effect of NSAID is that, the funds represent the area of keratinizing squamous epithelium of the stomach of the rat. The epithelial cells of this region have tight apical junction making the mucosa impermeable to back diffusion of hydrogen ion, and thus more resistant to the effects of NSAID (21).

Body. Aspirin causes lesions in the body of the stomach in 100% of the cases, and these are represented by the following grades: grade 1: 0%, grade 2: 60% of cases, and grade 3: 40% of cases. Indomethacin affect the body by the same extent as aspirin (100%), but the lesions are severer than those produced by aspirin; grade 1in 0%, grade 2 in 40% of cases, and grade 3: 60% of cases. These findings can be explained by the fact that, the body of the stomach contains the largest number of acid

acid and pepsin-containing glands that when exposed to damage by NSAID will lead to more production of acid and pepsin, and thus more severe damage. Celecoxib affects the body in 100% of cases, however the degree of damage is less sever than that caused by aspirin or indomethacin; Grade 1 in 50% of cases, grade 2 in 50% of cases, and grade 3 in 0%. These results are consistent with those reported by Capple et al, (22).

Pylorus. Aspirin produced lesion in the pylorus by 100% of the cases and represented by the following grades: grade 1 in 0% of case, grade 2 in 20% of case, and grade 3 in 80% of cases.

Indomethacin produced lesion in the pylorus by 100% of the cases as following: grade 1 in 0% of cases, grade 2 in 50% of cases, and grade 3 in 50% of cases. These differences between aspirin and indomethacin in gastric toxicity can be explained by the fact that, aspirin is a potent inhibitor of COX-1 and COX-2. Suppression of prostaglandin synthesis via inhibition of COX-1 can cause an increase in gastric acidity, and a decrease in gastric and duodenal secretion of bicarbonate. In addition, aspirin is especially known for its ability to cause local toxicity through a mechanism known as ion trapping, in which the drug becomes concentrated in the mucosa (22). In this case, the aspirin may have caused further damage by increasing the overall acidity in the pylorus**.**

Recently (23), it has been shown that prostanoid synthesis is greater in pyloric mucosa than it is in duodenal mucosa, which means that Cox-1 is highly expressed in pyloric mucosa. Since Aspirin has a high ratio of Cox-1/ Cox-2 selectivity, its toxic effect on pyloric mucosa is more than that produced by indomethacine, though the later has more sever effect on the body than does aspirin.

Celecoxib affect pylorus by 70% of case as follow: grade 1 in 40% of cases, grade 2 in 60% of cases, and grade 3 in 0% of cases. This can be explained by the fact that the different percentage of induction of ulcer by different members of NSAIDs is due to different ratios of cox-1/ Cox-2 selectivity. Nonselective NSAIDs significantly decreased prostanoid concentrations in the pyloric mucosae compared with the effects of a selective COX-2 NSAID (24).

Conclusions:

Aspirin and indomethacine produced lesions in gastric mucosa by 100% of the cases. These lesions take the form of gastric erosion and ulceration, and involved especially the body and the pylorus of the stomach. These lesions are more severe than those produce by Celecoxib, and was mostly grade 2 and grade 3.

Aspirin produces more severe lesions in the pylorus than indomethacin (80% of grade 3; indomethacine 40% of cases grade 3), Indomethacin produces more sever lesions in the body than does aspirin, 60% of cases were of grade 3; while aspirin producesd grade 3 lesions in only 40% of cases.

Celecoxibe produces lesions that are confined to the body and pylorus, and these lesions are mostly of grade 1 and grade 2.

New generation of NSAIDs shows less gastric toxicity compared to traditional generation. Celecoxib is better tolerated by gastric mucosa, since it produced the least gastric lesions compared to aspirin and indomethacin.

References

1. Carson JI, Willet LR: Toxicity of NSAID: An overview of the epidemiological evidence. J Drugs 46(suppl.):243-248, 1993.
2. Gabriel SE, Jaak L, and Bombardier C: Risk of serious gastrointestinal complications related to NSAID. N Engl. J. Med 303: 136-138. 1980.
3. Wolf MM: NSAID and gastric mucosa. N Engl. J. Med.15: 37-48, 1996.
4. Shigeta JL, Takahashi S, Okabe S: Role of cyclooxygenase-2 in the healing of gastric ulcer in rats. J. pharmacol. Experiment 286: 1383-1390, 1998.
5. Kargman S, Charleson, Cartweigh M, et al: Characterization of prostaglandin G/H synthase 1&2 in rat, dog, monkey, and human gastrointestinal tract. Gastroenterology 111: 445-454, 1996.
6. Needleman P, Isakso PC: The discovery and function of Cox-2. Rheumatol.24 (suppl 49.): 6-8, 1997.
7. Gies GS: Update on clinical development with celecoxib; what can we expect? J. Rheumatol.26: 31-36, 1999.
8. Engelhard G, Homma D, et al: Anti-inflammatory, analgesic, antipyretic, and related properties of meloxicam a new NSAID with favorable gastrointestinal tolerance. Inflamm. Res. J: 423-433, 1995.
9. Ganong WF: Textbook of Medical Physiology. Appleton and Lang. Norwalk. Connecticut. 14th edition, PP88-89, and PP, 408-421, 1988.
10. Sun DC, Chen JK: Experimental ulcer production in the pylorus legated. J. Clin. Gastroenttrol. 27(suppl.): 21-27, 1998.
11. Cryer B, Gold Schmidt M, Redferm, et al: Comparison of salicylate and aspirin on mucosal injury and gastroduodenal mucosal prostaglandin. Gastroenterology 99: 1616-1621, 1990.
12. Vane JR, Mitchell JA, Appleton I, et al: Inducible isoform of cyclooxygenase and nitric oxide synthase in inflammation. Proc. Natle. Acad. SCI .USA 91: 2046 -2050. 1994.
13. Schema JM: Pathogenesis of gastrointestinal injury due to NSAIDs: Implication for prevention and therapy. Semin. Arthritis. Rheum. 21: 201-210, 1992.
14. Sarosiek J, Mazuta K, Slomiany A, et al: effect of acetyl salicylic acid on gastric mucin viscosity, permeability for hydrogen ion, and susceptibility for pepsin. Biochem.Parmacol. 35:4291-4295, 1986.
15. Goldstein KD, Correa MY, et al: Reduced incidence of gastrointestinal ulcer with celecoxib. American Journal of Gastroenterology 96 (400): 1020-1026, 2001.
16. Cryer B, Dubois A: The advantage of highly selective inhibitors of cyclooygyesase enzymes. Prot Lipid Med.56: 341-261, 1998.
17. Cannon GW: Cyclooxygenase-2 selective inhibition. Drugs Today. J. 35(7):487-496, 1999.
18. Brain D, Golden MD, Steven B, Abramson MD, et al: Selective cox-2 inhibitors for arthritis. J. of Rheumatology 21:1346-1349, 2000.
19. Tsujii M, Kawaka S, and Dubois RN: cyclooxygenase-2 expression in human colon cancer cells increases metastatic potential Porch Natl. Acad.SCI USA 112: 387-397, 1997.

20. Sachin Manocha, Venkataraman S: Pharmacological and histopathological evaluation of ulcer formation in aged rats. Gastroenterology. 130:1000-1013, 2000.
21. Vane JR, Botting RM: New insight in to the mode of action of anti-inflammatory drugs associated with upper gastrointestinal toxicity. Gastroenterology Clin North Am 29: 97, 2000.
22. Suma Reed: Non-steroidal anti-inflammatory drug-induced duodenal ulceration and perforation in mature Rottweiler. Can Vet J. 43(12): 971-972, 2002 December.
23. Wooten JG, Blikslager AT, Rayan KA, Marks SL, Law JM, Lascelles BD: Cyclooxygenase expression and prostanoid production in pyloric and duodenal mucosae in dogs after administration of non-steroidal anti-inflammatory drugs. American journal of veterinary research 69 (4):457-464. April 2008.
24. Shorrock CJ, Ress WD : Mucosal adaptation to endomethacin induced gastric damage. Gastroenterology 33:164- 169, 1992.

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