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Histological changes caused by using Celebrex on the stomach, small intestine, and liver of mouse

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Abstract: *The administrations of non- steroidal anti-inflammatory drugs (NSAIDs) are widely used due to their les adverse effects and good safety. Celebrex is one of NSAID which works by reducing enzymes that cause inflammation and pain in the body. Celebrex is used as an antipyretics, analgesics, and in the treatment of muscles aches. It also used for patient with rheumatoid arthritis to reduce pain as an anti- inflammatory agent for a long time. However, some recent studies have reported that rheumatoid patients have been identified for varying degrees of stomach, small intestinal bleeding, and liver injuries. This histological investigation helps to explain the adverse effect of Celebrex on the previously mentioned organs. The animals were divided to three groups, group A control, group B treated for four weeks, and group C treated for eight weeks. The treated groups were given an oral dose 0.2mg of Celebrex. The mice were sacrificed, and tissues from the stomach, small intestine, and liver were taken and fixed in 10% buffered formalin and stained with H&E for light microscope examination. The experimental groups showed histological changes ranging from few changes in the gastrointestinal tract to more severe ones, while the liver is more affected by the drug and showed more injury. The student's t test was used for statistic analysis.*

Keywords*: Celebrex, NSAIDs, side effects, Histological changes*

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I. Introduction

The administrations of non- steroidal anti-inflammatory drugs (NSAIDS) are the most commonly used drugs in inflammatory diseases because they are effective in the management of pain, fever, redness, and swelling arising as consequences of inflammatory mediator release and due to their efficacy and good safety profile (Suleyman*et al*., 2007).Both therapeutic and side effects of (NSAIDs) are dependent on cyclooxygenases (Cox) inhibition (Suleyman *et al*., 2007). Cyclooxygenase are enzymes that cause pain. There are two isoforms of Cox enzymes called Cox1 and Cox2 (Williams and Wilkins 2009) Celebrex is one of (NSAID); it works by reducing specific enzyme Cox2 that cause inflammation and pain in the body. The structure of Celebrex is $C_{17}H_{14}F_3N_3O_2S$ (PubChem, 2005).

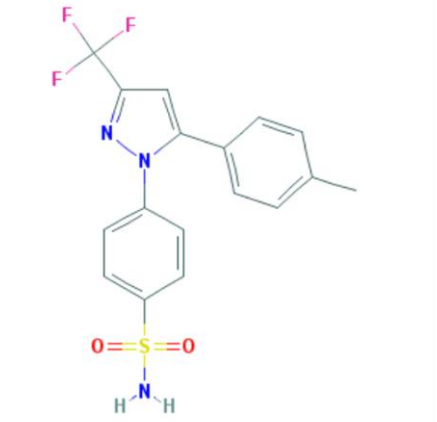

Figure 1. Structure of Celebrex

Celecoxib and rofecoxib drugs or their derivatives which belong to the same group have distinct physiological effects, and potencies which imply that there may be more than two or five of Cox isoform (Suleyman*et al*., 2007). Celebrex is one of the selective (NSAIDs) inhibitors group that works by reducing specifically the enzyme Cyclooxygenase-2 (Cox 2) (Suleyman *et al*., 2007).

Celebrex has several side effects but does not always happen to everyone. They can range from mild such as a headache, diarrhea, nausea, weight loss, allergic, and skin rash (Pub Chem, 2005) to severe like cardiovascular, gastrointestinal diseases, liver injuries, kidney and renal failure depending on individual cases (El Hajj *et al*., 2009; Cohen., 2003).

According to Chang *et al*., the frequency and severity of NSAIDs adverse effects have controversies specifically the effects on the gastrointestinal tract. Not only the above-mentioned changes but also the long – term complications, need more studies (Chang *et al*., 2011). Moreover, Somanath., (2014) reported that many studies suggested additional investigations on NSAIDs that mean there are few investigations of the side effects of Celebrex on the gastrointestinal tract and liver hepatotoxicity.

From the reports mentioned above, controversies existed between researches about the benefits verses risks using non-steroidal anti-inflammatory drugs. This investigation encouraged our search about side effects and benefits of Celebrex to be done.

II. Materials and methods

The tested drug

Celebrex was grounded and dissolved in water. The dose 0.2 mg was given orally daily to each group.

Hematoxylin and Eosin stain:

The basic stain that was used to stain histological specimens that contain negative charges such as ribosomes and chromatin-rich cell nucleus and the cytoplasmic region rich in RNA and stain them the blue or purple color, while the Eosin stain is an acid stain was used to stain histological specimens that contain positive charge such as protein. And cytoplasm stains them red or pink color. Hematoxylin & Eosin stain, Canada balsam, and paraffin wax all were obtained from Sigma-Aldrich Com., Louis, Missouri, USA.

Buffered formalin:

Neutral Buffered Formalin, 10% was prepared from stock solutions (NBF) which is useful as a fixative for photography specimens as it permits restoration of natural color to the specimen. Sodium dihydrogen phosphate, monohydrate (NaH2PO4.H2O) 4.0 g and Disodium hydrogen phosphate, anhydrous (Na2HPO4) 6.5 g were added (Drury, and Wallington, 2009). Sterile normal saline solution consists of 0.9% sodium chloride and water was prepared.

Tested animals

A total number of 54 adult male albino Swiss mice from MFI strain were used for 2-3 months old and weighed 30 ± 35 grams were used in this investigation. The mice were healthy not suffering from any disease or injury. They were purchased from the animal house of KFMRC in Jeddah.

The conventional animal basal diet was obtained from a grain mill in Jeddah. Each 100 g consists of the following: 12% protein (17.14 g 70% casein), 4 g corn oil (4% fat), 0.3 g methionine (0.3%), 0.2 g choline chloride (00.2 %), 4 g minerals (4% minerals), 1 g vitamin mixture (1% vitamin), 4 g cellulose (4% fiber), and 69.36 g corn starch (69.36%). The basal diet was stored in a dry place out of direct sunlight.

All the animal experiments were carried out under protocols approved by the Institutional Animal House of the University of King Abdulaziz at Jeddah, Saudi Arabia. The animals were housed 8 in each cage and received normal basal diet and tap water in a constant environment (room temperature 28 ± 2◦C, room humidity 60±5%) with a 12 h light and 12 h dark cycle. The animals were kept under observation for two weeks prior to the start of the experiment to exclude any undercurrent infection.

Grouping of mice:

Fifty-four adult mice were used in this research. The animals were divided into three groups, around thirteen animals in each group. Group A, represented the control group, group B, was given Celebrex for four weeks, and group C, was given Celebrex for eight weeks. Six mice of each group A and group B were sacrificed at the period of four weeks; six mice of group A and group C were sacrificed at the period of eight weeks.

At the end of the experiment, rats were sacrificed using ether anaesthesia by cervical dislocation, and then the abdomen was dissected and one kidney and a piece of the liver and intestine were saved in saline buffer (0.9% NaCl) for histopathological investigations and used for examinations using light microscope.

Statistical analyses:

Comparisons between groups were made by student's t test. Group A was control, group B was treated for four weeks, and group C was treated for eight weeks. Differences between groups of $p<0.05$ was considered significant.

III. Results

Fifty-four mice were used in this research, they were divided into three groups, group A was control one, group B was treated with Celebrex orally and daily and all animals were sacrificed after four weeks (group B) or eight weeks group (C) and were compared with group A.

Light microscopic examinations of mouse liver control presented well-defined hepatocytes radiating from the central vein. Some hepatocytes are binucleated **(**Figure 2A). Light microscopic examinations of adult mouse liver sections of group B showed congested central vein with slightly disrupted lining membrane (Figure 2B).While group C livers showed highly congested central vein with blood and opening into three sinusoids. Also, the sinusoids were congested. Its lining epithelium disappeared in some parts and other parts were normal shape (Figure 2C).When compared group B and group C with group A there were no significant differences. The p= 0.10 for group B and p=0.36 for group C. There were some changes but not significant because p>0.05. Also, comparing group B with C, p= 0.31 there were some differences but not significant because the p>0.05 (Table 1).

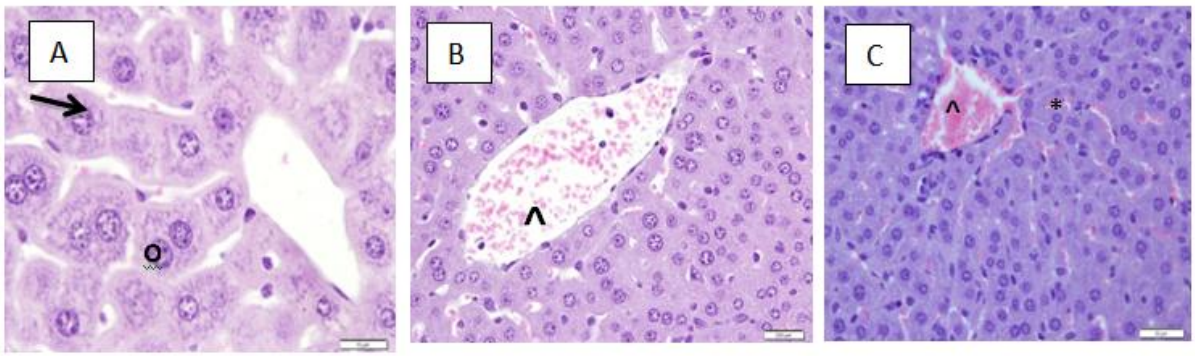

Fig. 2: A: Liver of control showed radiation of hepatocytes from central vein, B: Treated liver for four weeks with Celebrex showed some hepatocytes lost its radiation, and congested central vein and C: Treated liver for eight weeks with Celebrex showed hepatocytes lost its radiation, and highly congested central vein and sinusoids.

In another light microscopy examination of the stomach sections of group B, showed some columnar cells of the villi have normal shape while others had changed in shape and the mucosa layer became thick and lost its boundary. The gastric glands also had normal shape. In submucosa a blood vessel appeared congested with blood to the extend it invigilated into the muscular layer (Figure 3A). The treated stomach group C. showed few columnar cells still have a normal shape but more damaged columnar cells were observed compared to group B, the lumen was full of infiltrated cells containing small vesicular nuclei**.** Some glands were normal in shape, while the others were degenerated. The blood vessels were congested with blood. Also, the blood was infiltrated into the submucosa (Figure 3B).The control presented regular shape of the villi with the simple columnar epithelium was well defined. In the lamina propria the gastric crypts also were normal. The gastric crypts were seen clear (Figure 3C). Groups B and C were compared with the control, some differences were noticed but there were not significant. The p=0.32 for group B and p=0.72 for group C and it considered significant, p<0.05, while the differences between group B and C was significant, p=0.02 there were high degeneration because p<0.05 (Table 2).

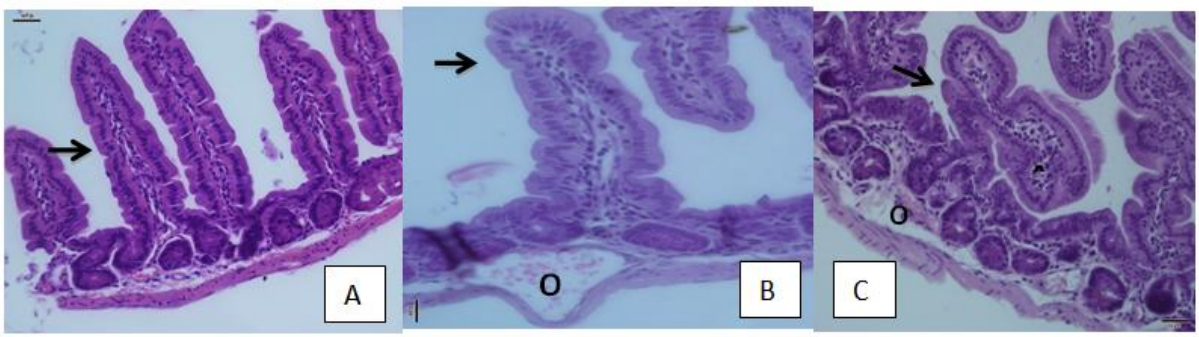

Fig 3: A: Stomach control showed normal shape, B: Treated stomach for four weeks showed effects on villi and there was congested blood vessels which invagenated to the muscular layer, C: Treated stomach for eight weeks showed two villi were fused together, with damaged of columnar cells and congested blood vessels were seen.

In small intestine light microscopy examination showed that glands were normal**,** highly congested blood vessels. The control showed the villi had a lot of goblet cells, which have role in protection. The glands were clear (Figure 4A). |Group B showed two villi were fused together, the columnar cells lost their borders while, some of the villi were in normal architecture. The lumen's contents of the two fused villi have some of infiltrated nuclei (Figure 4B) while, group C presented two villi started to fuse together and they completely lost their normal shape, borders and the top of the villi seemed to be sloughing off. There was an infiltration of blood in the lumen of the villi. Some glands were normal while others had damaged cells (Figure 4C).

The compared group B and group C with control (group A) were some changes. The p=0.24 for group B and p=0.31 for group C, these differences were not significant because the significant value was p<0.05. Also, the compared group B with group C, p= 0.29 were some differences but not significant because the p>0.05 (Table 3).

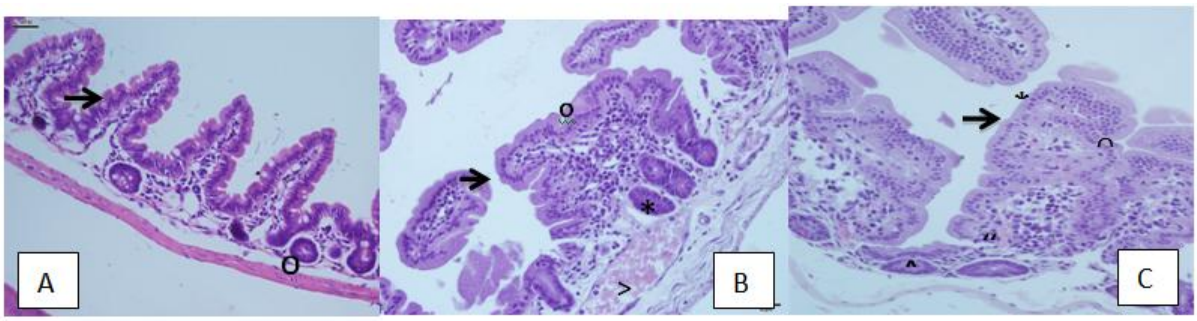

Fig 4: A: Treated small intestine for four weeks with Celebrex, showed damaged in columnar cells, two villi fused together, and highly congested blood vessels, B: Treated small intestine for eight weeks with Celebrex showed damage in cells, villi were shedding from the top, and infiltration of blood into the villi and C: Small intestine control showed normal structure and had lot of goblet cells.

Table 1: Damage of liver cells, used image J program. The compared were between group B and C with control and compared group B with group C.

Paired Samples Statistics						Paired Samples Test		
Tissue	group		N	Mean	Std. Deviation	t	df	P - Value
Liver	A	Baseline	3	211.22467	1.567231	2.804	2	0.107
	B	Week4	3	184.51933	16.324123			
	B	Week4	3	184.51933	16.324123	-1.348	2	0.310
	C	Week8	3	199.90333	18.211859			
	A	Baseline	3	211.22467	1.567231	1.168	2	0.363
	C	Week8	3	199.90333	18.211859			

Table 2: Damage of stomach cells, used image J program.The compared were between group B and C with control and compared group B with group C.

Paired Samples Statistics						Paired Samples Test		
Tissue	group		N	Mean	Std. Deviation	t	df	P - Value
Stomach	A	Baseline	3	146.69733	6.279915	1.294	2	0.325
	B	Week4	3	126.09933	24.636489			
	B	Week4	3	126.09933	24.636489	-6.959	2	0.020*
	C	Week8	3	151.62033	18.637744			
	A	Baseline	3	146.69733	6.279915	-0.401	2	0.727
	C	Week8	3	151.62033	18.637744			

Table 3: Damage of small intestine cells, used image J program. The compared were between group B and C with control and compared group B with group C.

Paired Samples Statistics						Paired Samples Test		
Tissue	group		N	Mean	Std. Deviation	t	df	P - Value
Small intestine	A	Baseline	3	174.16233	20.094963	1.629	2	0.245
	B	Week4	3	143.91500	16.504947			
	B	Week4	3	143.91500	16.504947	-1.413	2	0.293
	C	Week8	3	152.46200	8.867613			
	A	Baseline	3	174.16233	20.094963	1.320	2	0.318
	C	Week8	3	152.46200	8.867613			

IV. Discussion

The non-steroidal anti-inflammatory drugs NSAIDs are a group of drugs that are used as antipyretic, analgesic, and anti-inflammatory activity (Chang *et al*., 2011;Wiliams and Wilkins., 2009). There were two kinds of NSAIDs selective and non-selective. NSAIDs work on special enzymes called cyclooxygenases (COX) enzymes that have two isoforms cyclooxygenase1 (COX1) and cyclooxygenase2 (COX2) (10). COX enzymes are required for the biosynthesis of prostaglandins (Wiliams and Wilkins, 2009).

Celebrex is one of the selective NSAIDs that work on the COX2 enzyme which stimulates inflammatory responses, using Celebrex as a selective NSAID inhibitor of COX2 which decrease prostaglandin productions leading to fewer benefits and unwanted effects of it (LiverTox, 2017; Wiliams and Wilkins, 2009).

According to Food and Drug Administration (FDA), the NSAIDs and Celebrex have the similar unwanted effects such as increased risks of the gastrointestinal tract (GI) like bleeding, ulcer, and perforation of stomach (Wiliams and Wilkins, 2009).

In this investigation, Celebrex was used for two periods of time, four weeks (B) and eight weeks (C). The tissues of the liver of albino mice represented with histological changes in both groups B and C. The histological changes in group B using Celebrex showed varying degrees of liver injures but not as severe as group C.

In the current study, the light microscopic examination of liver treated group B showed some hepatocytes lost their usual architecture which was the arrangement of hepatocytes in plates and radiating from the central vein, and others lost their borders. But other hepatocytes had their normal pattern of arrangement. Some of the central vein and sinusoids were congested with blood and other sinusoids seem to be fused together.

In our results, the group C treated liver presented more side effects than group B. the laboratory examination for group C showed the hepatocytes have an irregular pattern from the usual liver. The hepatocytes lost its borders, and the nuclei lost its normal shape. Also, some nuclei aggregated with no boundary between them and the sinusoids were congested with blood. In other specimens, the central vein and portal vein are highly congested with blood, and they lost some its lining epithelium. In agreement with our study, (Kockaya *et al*., 2010) suggested that Celebrex has degenerative effects on liver leading to histopathological changes in liver tissues. Also, they mentioned that, the histological examinations observed mononuclear cell infiltration, hyperplasia and cellular degeneration in liver which, occurred in our results. On contrast to the results in this study, (Gao *et al*., 2013) suggested that Celebrex was safe to use and does not make severe liver injury.

Microscopic examination of specimens of the group C, treated stomach of adult mouse showed that the different degenerative parts of villi became thickened and some of mucosal columnar cells lost its boundary. Also, congested blood vessels were observed in submucosa and invaginated to the muscular layer. In group C stomach examination showed that the adjacent gastric villi fused together in an abnormal shape while some columnar cells lost its normal shape. Also, inside the two fused villi, there were some small vesicular nuclei and there was a congested blood vessel at the base of the lumen.

In our study, the villi of the specimens of group B had an irregular shape and the cells lost its normal shape and boundaries. The lumen of villi contained small vesicular nuclei. In another specimen, two adjacent villi were fused to gather, and the lumen had an amount of infiltrated cells. Also, the blood vessels were highly congested with blood while the glands were in normal shape.Several studies reported that the NSAIDs has serious effects on gastrointestinal tract such as bleeding, ulcer, and perforation that can happen at any period of time with or without warning symptoms (Chang *et al*., 2011). (Takashi *et al*., 2006) mentioned that the adverse events of GI by using (NSAIDs) and Celebrex. COX2 inhibitors like Celebrex and rofecoxib are associated with unwanted side effects on gastrointestinal tract including bleeding, apoptosis of gastric cells.

Some studies had reported that, the selective COX2 inhibitors had new pharmacological advantages like reducing GI disorders about in half compared with NSAIDs. In addition, COX2 inhibitors such as Celebrex decrease the tumor size of intestinal polyps (Takashi *et al*., 2006). In agreement with our study, (Khalek2013) presented that NSAIDs had benefits of decreasing the inflammation and management of pain, but also it has several side effects, not only damages in the stomach and small intestine but also extend to the rest of body.

V. Conclusions

Non-steroidal anti-inflammatory drugs with both groups selective and non-selective had adverse effects and good safety profile for pain management. Oral selective inhibitors of NSAIDs such as Celebrex was associated with varying degrees of unwanted effects on the histological structure of the liver, stomach, and small intestine. The severe effects of Celebrex on the previous mentioned organs was including hemorrhages, ulceration, perforation of the stomach, small intestine, and toxicity and injuries of theliver. Clinicians and patients should be aware of the fact which is benefits versus risks.

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