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Comparative study of the effect of some new naproxen derivatives on the liver and kidney tissues of mice

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Abstract

Naproxen is a phenyl propionic acid that has, anti-inflammatory, analgesic and antipyretic effects with confirmed adverse effects on most body organs involve the stomach, intestine liver, and kidneys. Often produce significant gastrointestinal, liver and kidneys tissues ulceration and bleeding, particularly in elderly patients and patients with certain co morbidities. This study aimed to assess the analgesic effects of new naproxen derivatives (which were synthesis in other study) and limitation side effects *via* modifying their chemical structure by addition active groups to parent compound.

First step: Analysis of newly synthetized and administered naproxen-derived drugs on male albino mice (30-35 g) and distributed into five groups, the first-named negative control group. The four other groups which administered one of the synthetized compound of naproxen derivatives.

The current study reported that the histopathological section of hepatocyte of mice treated orally with 250 mg /kg of naproxen for 5 days showed severe dilatation and congestion of central vein with necrosis of hepatic tissue with amyloid deposition in necrotic hepatic tissue with lymphocyte and Kupffer cells infiltration. On the other hand, the histopathological section of the liver of mice treated orally with 250 mg /kg of compound for 5 days showing severe distraction and hemorrhage of hepatic tissue, while compound 5 showed severe necrosis of hepatic tissue and vacuolation as well as, necrosis of hepatic tissue and inflammatory cell infiltration in rats. Compound X2. While the results revealed clear improvement in of liver of mice who received compound *via* regeneration of hepatic tissue by the formation of multiple granulomas around the newly formed blood vessels as well as immune cell stimulation. In addition to naproxen appears amyloid deposition in necrotic renal tissue while orally appears regeneration of destructive tissue by the formation of granuloma around newly formed blood vessels.

In conclusion our research concludes that related new derivative is a valuable focus for future seeks and potentially clinical implementation, due to its relatively high efficacy and minimal adverse effects in comparison to another tested compound in our study.

Keywords

Naproxen • Liver • Kidney • HNMR • Anti-inflammatory

Introduction

The first use of NSAIDs goes back more than 3,500 years. The anti-inflammatory drugs has begun used to control Pain, firstly by Salicin was initially identified by1828 that confirmed its anti-inflammatory performance. In addition to two years after Clinical trials with small doses, Bayer management determined to begin Production and release of aspirin, as a drug has an analgesic for control pain and blood thinner in a hypertensive patient. There are many families of cyclooxygenase (COX), also named prostaglandin endoperoxidase synthase enzymes, which was first documented by many researchers in the last century. the studies confirmed two enzymes are (COX-1)

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and cyclooxygenase-2 (COX-2) , in fact, the toxicity and adverse effects related to NSAID use have been a role in COX-1 inhibition [1].

COX-1 is current under fundamental conditions in different cells involve renal marrow collecting ducts Endothelial cells, cells of the mucosal layer in the gastrointestinal tract, platelets, and Interstitial. COX-2 isoform It is physiologically current at minimum concentrations in smooth muscle cells macrophages, fibroblasts monocytes, and chondrocytes, but is also formative in some tissues, such as the duodenal mucosa, kidneys, and brain. Moreover, COX-1 is one of the constituent isoforms basically overexpression through the physiological state, and Expression of COX-2 is stimulated under specific pathological conditions, such as after excitation of IL6,TNFa as inflammatory cytokines or insinuation to a natural toxin such as lipopolysaccharide (LPS) of salmonella. NSAIDs in veterinary medicine are considered effective in managing Pain and other discomforts related to oral surgery and do its curative effect by prohibit Cyclooxygenase (COX), which block prostaglandins output that synergistic interactions with others remedies promoting local inflammatory reactions and huge pain. Naproxen is one of derivatives of a phenyl propionic group having analgesic activity, anti-inflammatory and control of hyperthermia. Such activity via support inhibition complex prostaglandin synthetase enzymes that lead to limitation of generation of prostaglandins from pathway of arachidonic acid. The exact mechanisms by which NSAIDs induce gastrointestinal ulcer and bleeding is by damage of the tissue surface barrier to gastric acid and cytotoxic, in addition to NSAIDs reduced Mucus, bicarbonate layer, blood flow, cell renewal that consider as defense mechanism.. The stomach has mucus gel layer possess hydrophobic character via the synthesis and secretion of surfactant-like phospholipids. Some study modify NSAIDS chemical structure to reduce HARMFEL effect on GIT mucosa, one of these suggested formulated naproxen with phosphatidylcholine and showed clear reduction in GIT injury and limited hemorrhagic ulcer without anti-inflammatory and COX-inhibitory activity. The addition of material assistance to the foundation material may alter the effectiveness of the qualities and material basis. Change may be a positive direction and thus reduces the harmful effect on GIT with potentiate analgesic and ant inflammatory properties. One of the pathways of protect themucosa of GIT tract, this by conserve on amount of prostaglandins that act as cytoprotective. The current study aimed to improve Naproxen by increasing its analgesic effect and minimize its adverse effects by modifying the parent naproxen by adding new compounds for formulation new drugs. The current study aimed to evaluate the efficacy of new synthetic chemical agents derived from naproxen by adding chemical groups to standard naproxen as well as evaluate the safety of new compounds on gastrointestinal tissue. By modifying the naproxen, we hoped to generate new drugs that display clinically better properties than reference naproxen. This is the ability to produce antiinflammatory, antipyretic with minimal side effects than NSAIDS [2].

Synthesis of New compound from naproxen

Interaction scheme: The current study aimed to evaluate the efficacy of new synthetic chemical agents derived from naproxen by adding chemical groups to standard naproxen as well as evaluate the safety of new compounds on gastrointestinal tissue. By modifying the naproxen, we hoped to generate new drugs that display clinically better properties than reference naproxen. This is the ability to produce antiinflammatory, antipyretic with minimal side effects than NSAIDS (Figure 1).

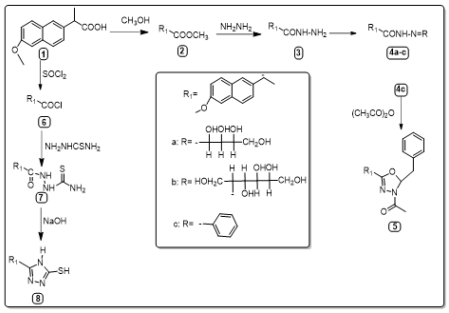

Figure 1: Show synthesized new compounds from naproxen drug.

Materials and Methods

Series of new naproxen derivatives which were synthesized in one of our previous studies as in Scheme 1.

Thirty healthy male albino mice weighing 25-30 grams were purchased from the laboratory animal house of the University of Baghdad and randomly divided into six groups, each group containing five mice placed in polypropylene cages. Mice were maintained at room temperature and under environmental conditions for nearly 8-12 h in the light-dark cycle). All animals were acclimatized for two weeks to animal house conditions before beginning the experimental protocol, taking into account the diet in the form of pellets and water given ad libitum.

After two weeks of days of adaptation, mice were randomly divided into six groups as follows: group 1: negative representation of the control group, this group was given only distilled water group 2: positive control group for evaluate induced stomach ulcer of naproxen after an overnight fast. group 4: after an overnight fast, animals (20 mg/kg) received compound 5 for evaluate induced stomach ulcer group 5: after an overnight fast, the animals (20 mg/kg) received compound 4b for induced stomach ulcer group 6: after an overnight fast, the animals received 20 mg/kg of compound 4b for evaluate induced stomach ulcer.

Histopathological examination

The stomachs of sacrificed mice were taken, washed with normal saline, and then immersed in 10% formalin solution. The fixed samples were then trimmed, washed and dried in ascending degrees of alcohol. Samples were then flushed in xylol, embedded in paraffin, cut to 4–6 µm thickness and stained with (H and E) stain for gastrulation as described by Carlton, (1979).

Result and Discussion

The usage of nm identified to the in biochemical and chemical synthesis, the diagram confirmed showed the is clear difference in function groups between tested compounds. Painkiller and anti-inflammatories relieve pain and reduce inflammation and hyperthermia in humans and animals as symptomatic therapy. These agents are effective in joint and muscle pain and headache, but they are not efficient in clear visceral organ pain. This is due to the

powerful inhibitory prostaglandins transmitter that is accountable for the sensation of distress and inflammation as well as for control body temperature (Figures 2-5).

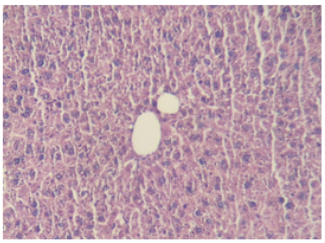

Figure 2: Histological section for control group of liver of mice showing the normal histological stricture. (H and E) X10.

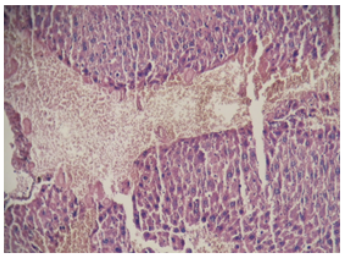

Figure 3: Histopathological section of liver of mice treated orally with250 mg /kg of 4a for 5 day showing severe distractions and hemorrhage of hepatic tissue (H and E) X 10`

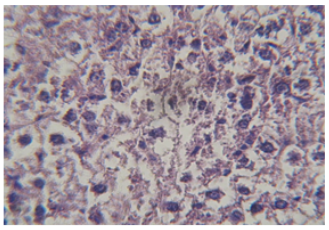

Figure 4: Histopathological section of liver of mice treated orally with 250 mg /kg of 5 for 5 day showing sever necrosis of hepatic tissue and vacuolation .(H and E 400X)

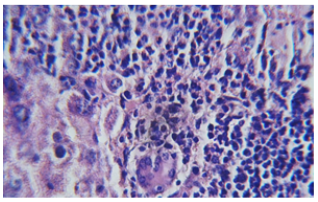

Figure 5: Histopathological section of liver of mice treated orally with250 mg /kg of 8 for 5 day showing necrosis of hepatic tissue and inflammatory cell infiltration mainly lymphocyte and giant cell ,with present of kuppfer cell .(H and E 400X)

High doses of NSAIDS or long-term therapy enhancement the risk of gastro duodenal injury, ulcers, gastric bleeding. Clinical therapy used to minimize NSAID-injury to duodenal injury by conventional drugs such as omeprazole has been shown to effectively reduce GI damage. But modern animal studies indicate that block acid secretion can worsen NSAID-induced gastric injury, liver damage, and kidney dysfunction (Figures 6-9).

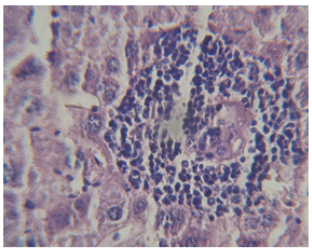

Figure 6: Histopathological section of liver of mice treated orally with250 mg /kg of 4b for 5 day showing formation of early granulom.(H and E 400X)

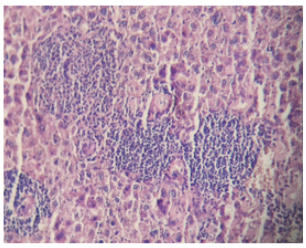

Figure 7: Histopathological section of liver of mice treated orally with 250 mg /kg of 4b for 5 day showing regeneration of hepatic tissue by formation of multiple granuloma around newly formed blood vessels .(H and E 400X)

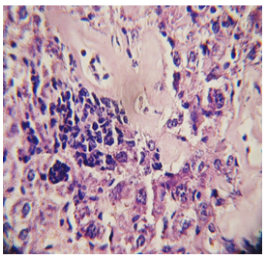

Figure 8: Histopathological section of liver of mice treated orally with 250 mg /kg of naproxen for 5 day showing amyloid deposition in nicrotic hepatic tissue with lymphocyte and kupffer cell infiltration .(H and E 400X)

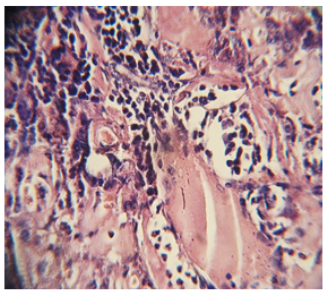

Figure 9: Histopathological section of liver of mice treated orally with250 mg /kg of naproxen for 5 day showing amyloid deposition in necrotic hepatic tissue with lymphocyte and kupffer cell infiltration .(H and E 400X)

The current study reported that histopathological section of hepatocyte of mice treated orally with 250 mg /kg of naproxen for 5 day showed sever dilatation and congestion of central vein with necrosis of hepatic tissue with amyloid deposition in necrotic hepatic

tissue with lymphocyte and kupffer cell infiltration. Moreover, the histopathological section of the liver of mice treated orally with 250 mg /kg of for 5 days showing severe distractions and hemorrhage of hepatic tissue, while damage was showed more prominent in the comp. 5 group to recorded severe necrosis of hepatic tissue and vacuolation [3]. In addition to the tissue of hepatocyte of liver of mice treated orally with 250 mg /kg of 8 for 5 days showing necrosis of hepatic tissue and inflammatory cell infiltration mainly lymphocyte and giant cell, with the presence of kuppfer cell (Figures 10-14).

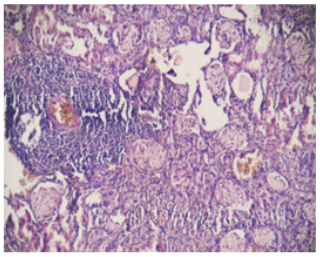

Figure 10: Histopathological section of kidney of mice treated orally with250 mg /kg of naproxen for 5 day showing amyloid deposition in necrotic renal tissue with perivascular cuff cell .(H and E 100X)

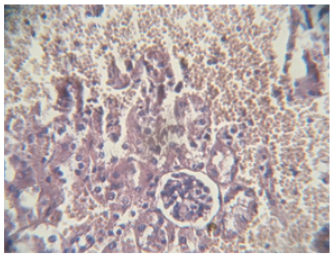

Figure 11: Histopathological section of kidney of mice treated orally with250 mg /kg of 8 for 5 day showing necrotic and hemorrhage of renal.(H and E 400X)

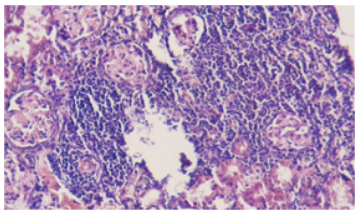

Figure 12: Histopathological section of kidney of mice treated orally with250 mg /kg of for 5 day showing regeneration of destructive tissue by formation of granuloma around newly formed blood vessels .(H and E 100X)

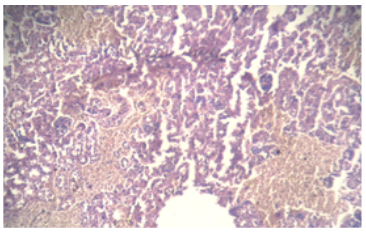

Figure 13: HistopathologicalF section of kidney of mice treated orally with250 mg /kg of 5 for 5 day showing sever necrosis and hemorrhage.(H and E 100X)

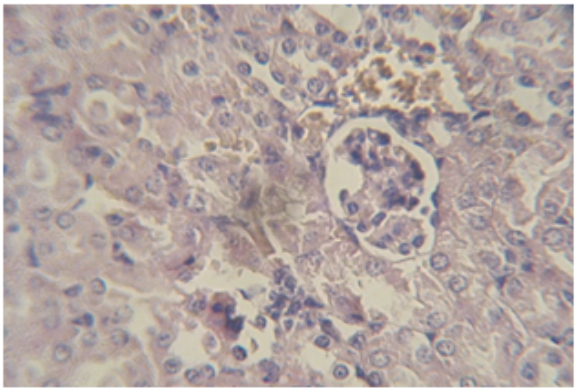

Figure 14: Histopathological section of kidney of mice treated orally with 250 mg /kg of for 5 day showing degeneration and necrosis of renal tubules and glomeruli ,with hemorrhage .(Hand E 100X)

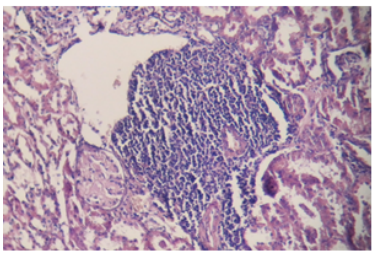

Figure 15: Histopathological section of kidney of mice treated orally with250 mg /kg of for 5 day showing regeneration of destructive tissue by formation of granuloma around newly formed blood vessels .(H and E 100X)

Moreover our data showed clear improvement in of liver of mice who received compound *via* regeneration of hepatic tissue by the formation of multiple granulomas around newly formed blood vessel. The present study support by other previous study showed that group was most clear and revealed perfect number of goblet cell in small intestine with encouragement of secretion a mucin seen in the lumen with infiltration of mononuclear cell with lymphoid tissue that give indicate of good chance for boost immune tissue and resistant ulcer. Our data indicate that a synthesis new compound and added an active group that increases analgesic activity was in agreement with indicating that Naproxen Phosphatidylcholine (Naproxen-PC) showed improvement in anti-inflammatory and COX- block activity and minimize GI injury and ulceration in two rodent models. In fact, COX inhibitory activity may be high for the modified naproxen than the parent naproxen, and it may be highly effective in decreasing pain sensation through the strong inhibition of arachidonate cyclooxygenase and thus the inhibition of prostaglandin releasing [4]. Histopathological section of kidney of mice treated orally with 250 mg /kg of naproxen for 5 days showing amyloid deposition in necrotic renal tissue with perivascular cuff cell. Our data reported that the histopathological section of kidney of mice treated orally with 250 mg /kg of for 5 days showing regeneration of destructive tissue by the formation of granuloma around newly formed blood vessels. However, very limited information is available on the renal safety of these compounds. In the current study indicates that naproxen, using in during a short period of medication, affects adversely the function of renal the renal *via* increased release of the renin-angiotensin

system. Cyclooxygenases (cox-1 and cox-2) are key enzymes in prostaglandin biosynthesis and the target enzymes for the commonly utilized nonsteroidal anti-inflammatory drugs [5].

Conclusions

The current study concluded that new derivatives have perfect anti-inflammatory and antipyretic with very mild influence on liver and kidney tissues.

Etthical Approval

The research has been approved by ethical commission of veterinary medicine according to no: 533fd2.

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