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Full Length Article

Evaluation of Cyclooxygenase Inhibitors on Biochemical Parameters and Renal Histopathological Changes in Rabbit

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Abstract

The aim of this study was to assess the effect of piroxicam and diclofenac on biochemical parameters and renal histopathological changes in rabbits. For those 18 rabbits were divided into three equal groups. injected intramuscular 3.0 mg/kg/day of piroxicam and diclofenac sodium, respectively. Blood samples were collected on 0, 5, 10 and 15 days (Treatment Phase) and 20, 25 and 30 days (Recovery phase). The statistics results showed that level of urea injected with piroxicam to group B, highly significant *(P < 0.01)* on days 10 and 15 and decreased on 25 and 30 days. Injected diclofenac to group C recorded highly significant *(P < 0.01)* on days 10, 15 and 20 and decreased on days 25 and 30. Injected piroxicam to group B level of creatine was recorded non-significant *(P > 0.05)* on days 5, highly significant *(P < 0.01*) on days 15, 20 and decreased on days 30. Injected diclofenac to group C showed, highly significant *(P < 0.01)* on days 15 and significant increase *(P < 0.05)* on day 10 and 30. Injected piroxicam to group B, recorded highly significant *(P < 0.01)* level of ALP on days 10. however, significant *(P < 0.05)* increase on days 15, 20, 25 and 30. Injected diclofenac to group C recorded a highly significant *(P < 0.01*) on day 10 and 15 and found significant *(P < 0.05)* increase on 20 and 30 days as compared to control group. Histopathological findings showed that injected diclofenac in group C were seen renal shrinked glomerulus, widened Bowman's space and vasoconstriction arteriole, injected piroxicam showed mild dilation of distal and proximal convoluted tubules, marked shrinkage of glomerulus and mild inflammatory cellular infiltration and hyperaemia in intratubular spaces were seen in group B. Concluded from present study that at similar doses piroxicam exerted less severe changes in the biochemical parameters as compared to diclofenac, which is also revealed in renal histopathological findings, that marked lesions were noted in diclofenac treated group either on day 15 or 30 as compared to Piroxicam in treated group.

Keywords: Cyclooxygenase inhibitors; Diclofenac; Histopathological structure; Piroxicam; Rabbits

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) constitute a heterogeneous compound of medications, which has role in analgesic, antipyretic, inflammatory resolution and healing enhancement as well. It is most regularly utilized medication and it was reported that these drugs have been used by 1% of the population every single day and are utilized by right around 30 million patients throughout the world (Ahmad *et al.* 2017). They are classified into two large categories steroidal and non-steroidal. Recently, different commercial products of NSAIDS are available in the veterinary field, without sufficient information about their side effects on the hematobiochemical parameters in animals (Darwish and Eldakroury 2020). NSAIDs act by blocking both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and along these combinations of prostaglandins and thromboxanes, which prompts the hindrance COX-2 and mitigating, pain relieving and antipyretic impacts are produced. The NSAIDs which restrain COX-1, are involved in gastrointestinal draining and ulcers (Ibrahim *et al.* 2019). It is reported that treatment with NSAIDs resulted in hepatic, gastrointestinal and renal affections (Fruchter *et al.* 2011). NSAIDs are well known for producing injuries to the stomach (disintegration and ulceration), the duodenum, liver, kidney and small intestine (Ogueji *et al.* 2018). The most clinically used medication from NSAIDs family is aspirin, ibuprofen, naproxen, diclofenac, piroxicam and meloxicam (Ivanova *et al.* 2015).

Piroxicam medication has been perceived for its quality as a chemoprotection in perpetual musculoskeletal and joint issues. It is synthetically remarkable, long-acting,

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strong pain-relieving and different maladies throughout the world. Laboratory tests have uncovered that in different animal models, Piroxicam restrained cell movement into an aggravated site along with diminishment of irritation (Warden 2010).

Diclofenac is (NSAIDs) and both are mostly used in clinics in pain management (Abdel-Rahman and Abdel 2021) including, conditions such as osteoarthritis, rheumatoid joint pain, ankylosing spondylitis, renal colic, dentistry and in preoperative and postoperative treatments (Bhagar *et al.* 2003). Usage of these medications produced moderate to steeped level of nephrotoxicity in light of the fact that kidneys are included in discharge of these agents, when contrasted with meloxicam, diclofenac sodium brought about a high level of nephrotoxicity (Nwangwa *et al.* 2018). However, the harmful impacts of diclofenac and meloxicam on kidney in human and animals are extremely normal (Adeyemi and Olayaki 2018).

NSAIDs has been reported one of significant reasons for decreased vulture population in south Asia. The reason of motility is used of diclofenac in animals. Died animals are feed of the vulture, so the laboratory test indicated that residue of diclofenac is accumulated in the kidney (Manimekalai *et al.* 2019). It was reported that differential influences of the piroxicam on renal capacity might be brought about by differences in pharmacokinetics between the frequency and dose utilized. Both these drugs have short half-lives yet have distinctive initial beginning measurements and recurrence of dosage is prescribed (Stempak *et al.* 2002).

Irrespective of pharmacokinetics of these two medication classes, the motivation behind this study to analyze the impacts of these agents on renal capacity as normally recommended and demonstrated for use by the Food and Drug Administration. So far, no relative study has been completed on the harming impacts brought about by Piroxicam and Diclofenac drugs, hence this study has been intended to analyze different unfavorable impacts of Piroxicam and Diclofenac of various serum biochemical parameters and kidney capacity and its histological structure in rabbits.

Materials and Methods

Animals and study design

For the experiment 18 adult healthy rabbits under the age of 2 months and weighing between (2–2.5 kg) were used. The procedure of experiments involving animals was approved by the ethical committee Sindh Agriculture University, Pakistan. And the protocol approved No. DAS/381/2016. The rabbits were kept in controlled conditions (temperature 17–23°C, humidity 45–60%) at Animal House, Sindh Agriculture University Tandojam, Pakistan. The rabbits were allowed two weeks of acclimatization period. The rabbits were offered fresh vegetables, grass and water *ad libitum.*

Treatments

Diclofenac sodium (Merck company) and piroxicam (Merck company) were used for parenteral administration (Intramuscular IM). The selected muscle sites are thigh muscles (gluteus medius), gluteus superficial and quadriceps femoris (lateral thigh) with needle size 21 gauge. The rabbits were randomly divided into three groups *i.e*., A, B and C (n = 6). Group A (Control) were fed with fresh vegetables (cabbage, carrot), grass and water. Groups B and C were treated with 3.0 mg/kg/day of Piroxicam and diclofenac sodium with fed with fresh vegetables (cabbage, carrot), grass and water, respectively daily for thirty days, rabbits in each group were tagged with different colored bands and marked 1 to 6 for all the groups for proper identification among groups.

Collection of blood samples

The experiment as designed for 30th days long through which blood samples were obtained at zero day (before start treatment) from all groups. Blood samples were collected for biochemical analysis during the 0, 5, 10 and 15th day of all groups (Treatment Phase) and 20, 25 and 30th days of experiment (Recovery phase).

The blood samples were taken from ear vein 3 mL of blood was collected from marginal ear vein of each rabbit by using a 26-gauge needle in EDTA tubes.

The serum was separated from blood by centrifuging machine at 1500 r.p.m for 10 min for biochemical investigation.

Biochemical parameters

Biochemical parameters urea, creatinine and ALP were evaluated from serum samples. Urea kit method (Human Company Germany) was used to determine urea. Serum creatinine was determined by using Jaffe Kinetic method (Live Diagnostic, Canada), Serum Alkaline phosphatase (ALP) was determined through kit method (Human Company Germany).

Histopathological examination

Half animals of each group were slaughtered on day 16th (end of the treatment) and half on day 30th (end of the experiment) applied slaughtered procedure of stun to neck cut. The kidneys were collected in 10% formalin for preservation. kidney was taken by making a longitudinal incision from posterior region to the front region. The histological examination was performed followed by Ahmad *et al.* (2017) briefly for fixation, the tissues samples were submerged in 10% neutral buffered formalin for 24 h, then embedded in the paraffin wax. Then, wax blocks were prepared. Next, the tissues were cut into 5 μm sections using a microtome. These tissue section slides were stained with

H&E (Harry's hematoxylin for 02 min and 1% eosin for 30 s) for examination by light microscopy using an compound microscope (10X, 40X) and photography was done.

Statistics analysis

The data is presented in (mean ± SD). Analysis of Variance (ANOVA) was applied to compare the significant differences between the groups using statistical package SPSS 11.5 (SPSS, IBM, Inc, USA, 2000).

Results

Effect of piroxicam and diclofenac on serum urea level

It was recorded that administration of 3.0 mg/kg doses of piroxicam and diclofenac on serum urea levels. The mean values of control (Group-A) were 23.45±0.67 mg/dL. Administration of piroxicam for 15th days to group B, highly significant increase *(P < 0.01)* on day 10th, 15th during treatment phase and significant increase *(P < 0.05)* on day 20th, during a recovery phase. The level of urea gradually decreased on 25 and 30th day *i.e.*, 27.30 ± 0.40 and 24.25 ± 0.57 respectively and was recorded as non-significant as compared to control groups. Administration of IM diclofenac to group C for 15th days recorded highly significant *(P < 0.01)* increase in the level of urea on day 10, 15 and 20th *i.e.*, 44.88 ± 1.52, 42.82 ± 1.79, 36.71 ± 1.06 respectively as compared to control values. The level of urea decreased gradually on day 25 and 30th *i.e.*, 28.93 ± 1.02 and 28.28 ± 1.16 respectively as shown in (Fig. 1).

Effect of piroxicam and diclofenac on creatinine

It was recorded that administration of 3.0 mg/kg doses of piroxicam and diclofenac on creatinine levels. The means values of control (Group-A) were 0.84 ± 0.01 mg/dL. Induction of piroxicam for 15th days to group B recorded as non-significant increase on day 5th, 0.92±0.04 however, creatinine showed significant increase *(P < 0.05)* on day 10th, 1.50 ± 0.01 post-drug administration. The level of creatinine revealed a highly significant *(P < 0.01)* elevation on day 15th, 20th, 3.85 ± 0.18, 3.08 ± 0.22 respectively and significant increase *(P < 0.05)* on day 25th, 1.38 ± 0.01. The value of creatinine gradually declined and almost returned to pre-treatment value and was found non-significant on day 30th, 0.94 ± 0.05 compared with control value. Administration of diclofenac to group C shows a statistically significant increase *(P < 0.05)* on day 10th 1.76 ± 0.18 post-drug administration. The level of creatinine with diclofenac increased significantly *(P < 0.01)* on days 15th, 20th, 25th, 5.51 ± 0.20, 4.84 ± 0.21, 4.48 ± 0.34 respectively and even remained significantly increased *(P < 0.01)* on day 30th, 2.51 ± 0.24 (Recovery phase) post-treatment as shown in (Fig. 2).

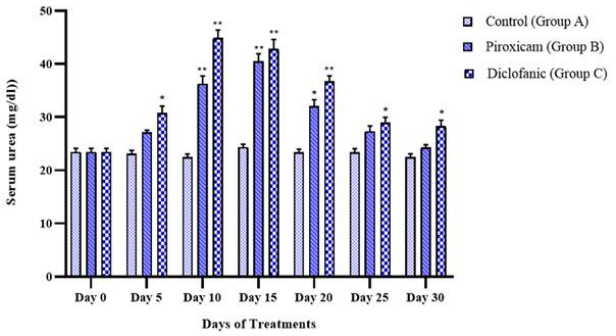


Fig. 1: Mean Serum Urea (mg/dL) of rabbits treated with piroxicam and diclofenac. Significant changes are indicated by *$P < 0.05$ and **$P < 0.01$ in comparison with control

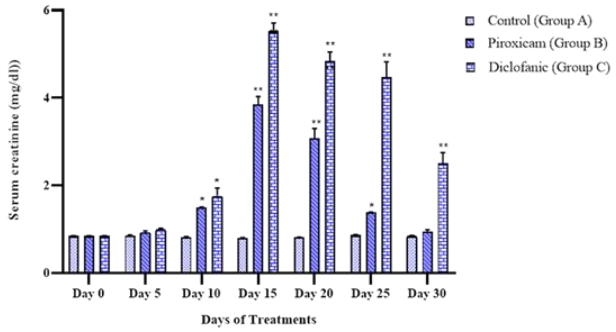


Fig. 2: Mean Serum Creatinine (mg/dL) of rabbits treated with piroxicam and diclofenac. Significant changes are indicated by *$P < 0.05$ and **$P < 0.01$ in comparison with control

Effect of piroxicam and diclofenac on serum Alkaline Phosphate (ALP)

It was recorded that administration of IM of piroxicam and diclofenac at 3.0 mg/kg doses serum ALP level. The means values of control (Group-A) were 123.69 ± 1.72 U/L. Administration of piroxicam to Group B, recorded non-significant increase on day 5th, 125.00 ± 0.87 and highly significant increase *(P < 0.01)* on day 10th, 133.66 ± 1.76. The level of ALP steadily decreased on subsequent days however, they were statistically significant *(P < 0.05)* on day 15th, 128.85 ± 1.80. During the recovery phase *i.e.*, day 20, 25 and 30th, 126.05 ± 1.16, 123.86 ± 0.58, 123.90 ± 0.49 respectively. The values almost returned to control value and were found to be statistically non-significant as compared to control value. Diclofenac administration to Group C on other hand recorded a highly significant *(P < 0.01)* increase on day 10 and 15th, 139.70 ± 2.77, 140.76 ± 1.84 during treatment, which remained persistently increased *(P < 0.05)* on day 20th, 130.58 ± 2.00 of the experiment. The level of ALP on day 25th, 126.51 ± 1.24 and 30th, 126.83 ± 1.20 was remained elevated and found significant *(P < 0.05)* as compared to control value as shows in (Fig. 3).

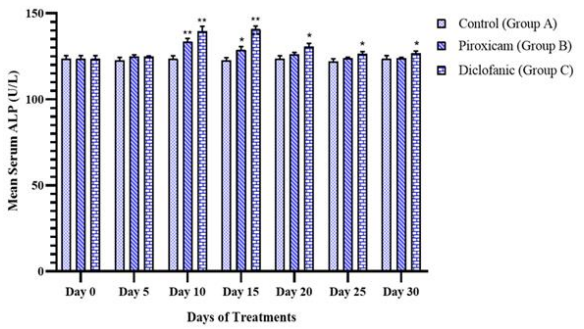
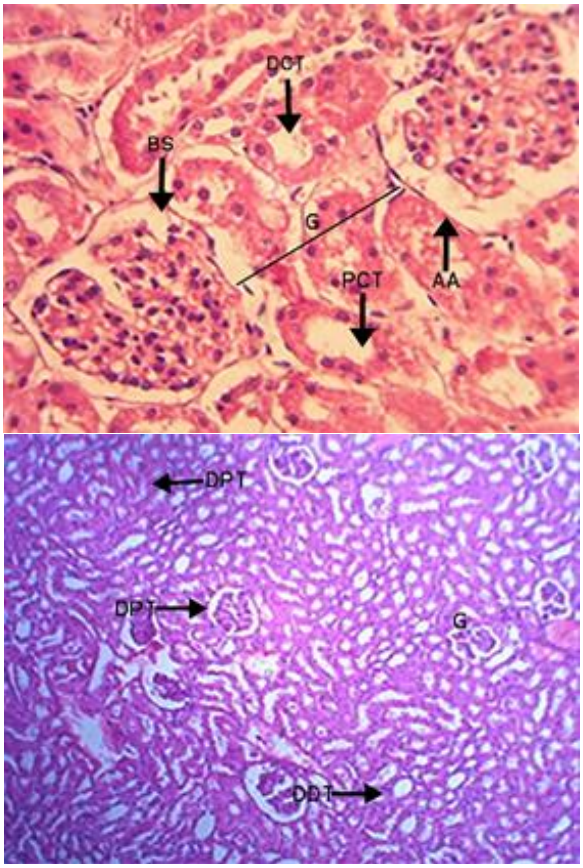


Fig. 3: Mean Serum ALP (U/L) of rabbits treated with piroxicam and diclofenac. Significant changes are indicated by $*P < 0.05$ and $**P < 0.01$ in comparison with control



Figs. 4 and 5: Renal section structure of control group A, Normal Glomerulus (G), Bowman's Space (BS), Afferent Arteriole (AA), Proximal Convoluted Tubule (PCT) and Distal Convoluted Tubule (DCT) Disrupted Proximal Tubules (DPT) and Distal Tubule Dilatation (DDT), (40X and 10X H&E)

Histopathological observation of renal tissues examination

Fig. 4 and 5 shows the kidney sections of control group (A). Glomerulus, bowman's space, proximal, distal convoluted tubules, disrupted proximal tubules and distal tubule dilatation were seen normal at (10X and 40X).

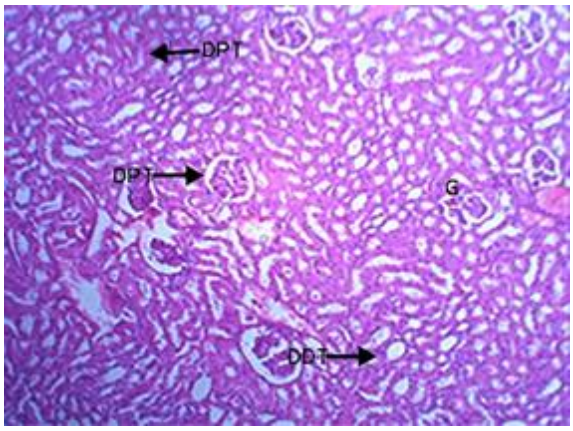


Fig. 6: Renal section of group B, Mild dilation of Distal Convoluted Tubule (DCT), Glomerulus (G) unchanged with a normal texture of bowman's space, (Day 15) (40X, H&E)

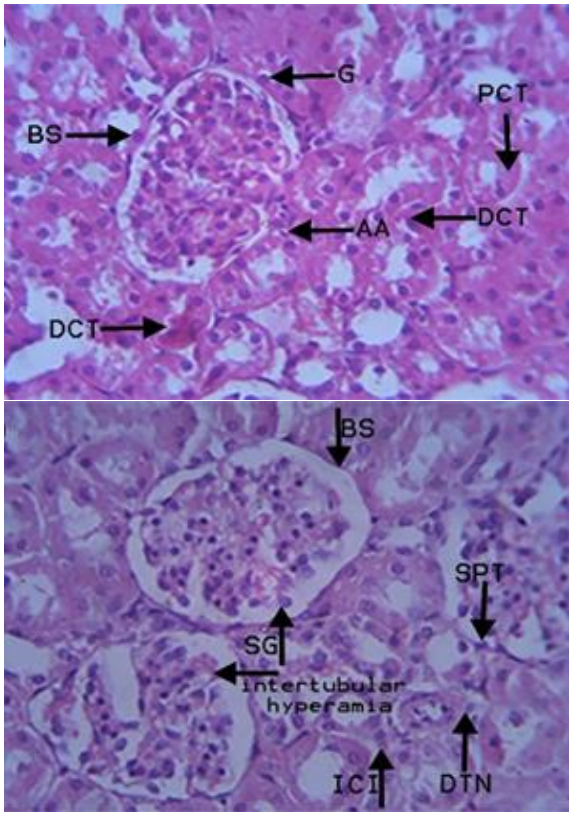


Fig. 7: Renal section of group B widened Bowman's Space (BS), Shrinked Glomerulus (SG), Inflammatory cellular Infiltration (ICI), Disrupted Tubular Nuclei (DTN), Swollen Proximal Tubules (SPT) and inter tubular hyperaemia (Day 30), (40X, H&E)

Effect of piroxicam on renal histopathology (day 15th and day 30th)

Fig. 6 and 7 indicate the renal sections of the rabbits

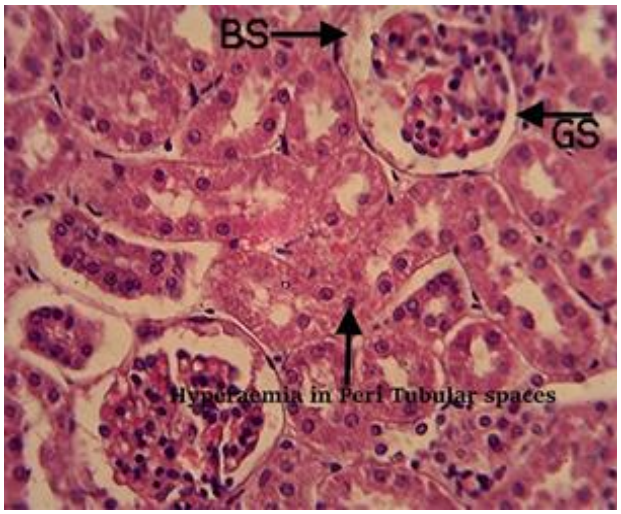


Fig. 8: Photomicrograph of renal section of group C, Shrinked Glomerulus (SG), widened Bowman's space (BS) and Hyperemia in Peri Tubular spaces (Day 15), (40X, H&E)

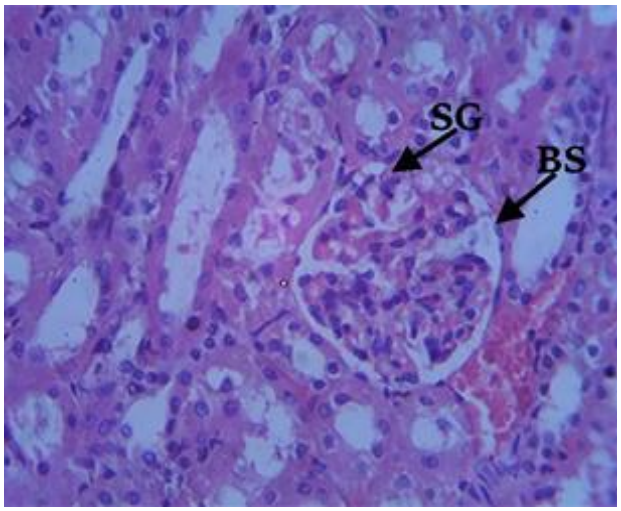


Fig. 9: Photomicrograph of renal section of group C, Shrinked Glomerulus (SG), widened Bowman's Space (BS) and Vasoconstriction of arteriole (Day 30), (40X, H&E)

administered with piroxicam (Group B) showed mild dilation of distal convoluted tubules and slight disruption of the proximal convoluted tubules. The glomerulus was seen to be unchanged with a normal texture of bowman's space. Marked shrinkage of glomerulus with widened bowman's space. The proximal convoluted tubules were appeared with obliterated lumens while distal convoluted tubules appeared to be congested with disturbed nuclei. Mild inflammatory cellular infiltration and hyperaemia in intratubular spaces were also seen.

Effect of diclofenac on renal histopathology

Fig. 8 and 9 show the renal sections of the rabbits administered with diclofenac (Group C) on day 15 were seen Shrinked Glomerulus, widened Bowman's space and Hyperemia in Peri Tubular spaces and Vasoconstriction of arteriole were seen at (Day 30), (40X, H&E). The results indicated that diclofenac caused more damage to the renal structures as compared to Piroxicam.

Discussion

Diclofenac sodium and piroxicam are two renowned NSAIDs which are commonly used during inflammatory conditions. Diclofenac sodium has been reported to be the predominant cause of vulture population drop in India and Pakistan up to 95% because of its accumulation in the carcasses of dead animals which caused kidney failure (Naidoo *et al.* 2009). As there is considerable interest in the toxicity of diclofenac in the past few years due to the illicit use of diclofenac in veterinary practice. Diclofenac and piroxicam comparatively because of its prevalent clinical use and possible dangers to the kidney structures, which is main organ involved in their excretion.

Among serum biochemical indices relating to kidney functions, serum urea of the rabbits of group B (Piroxicam) showed significant increase *($P < 0.01$)* only on day 10^{th}, 15^{th} and gradually decrease *($P < 0.05$)* on day 20^{th}. However, during the recovery period, the level of urea dropped off to almost control value and was found non-significant. Diclofenac on the other hand caused a highly significant *($P < 0.01$)* increase on day 10^{th}, 15^{th}, 20^{th} and were found significantly increased *($P<0.05$)* till day 30. With Piroxicam urea levels were found significantly increased *($P < 0.01$)* on day 10 and 15^{th} of the treatment however, this increase was transient and returned to almost control value and were found non-significant during the recovery phase of study. Piroxicam is NSAID of the oxicam class which has a non-selective inhibitory activity and a COX-1 to COX-2 ratio of 3.12 (Suleyman *et al.* 2007). Brater *et al.* (2001) reported that upon cessation of therapy, any deviations from the normal renal functions with almost all NSAIDS returns to baseline values. Diclofenac sodium non-selectively inhibits both COX-1 and COX-2 (Andalib *et al.* 2011). COX-1 possesses housekeeping functions and has a crucial role in maintaining renal blood flow. This persistent increase in urea level might be due to excessive concentration of Diclofenac which might have inhibited COX-1 resulting in decreased blood supply and with glomerular excretion of urea.

Diclofenac on the other hand caused significant difference *($P < 0.05$)* in serum urea level on day 10^{th}, which was followed by a highly significant increase *($P < 0.01$)* on subsequent days of analysis and continued till day 30^{th}. This was supported by Syed *et al.* (2012) who found significantly increase level of creatinine in rabbit model. Al-Maddawy and El-Ashmawy *et al.* (2013) stated that diclofenac related nephrotoxicity might be related with increased reactive oxygen species which induce pro-oxidative damage to renal tissues. Highly selective COX-2 inhibitor can also cause

renal problems, so one cannot be surprised with nephrotoxicity by a non-selective and devastating Diclofenac (Brater *et al.* 2001).

Creatinine is highly recommended as a diagnostic indicator for renal impairment and is considered highly specific for evaluating renal problems (Torres *et al.* 2013). In the present study significant increase *($P < 0.01$)* was observed in piroxicam treated rabbits (Group B) on day 15 and 20 and significant at *($P < 0.05$)* on day 25 however, on day 30 this increase was negligible and was non-significant as compared to control value. The increase in serum creatinine level during the treatment period may be due to the inhibitory effect of piroxicam (NSAID) on renal prostaglandins PGE2 and PGI2 resulting from COX-1 inhibition (Mahaprabhu *et al.* 2011), which drops off during the recovery period as the drug is eliminated from the plasma.

In our study ALP level in Piroxicam treated rabbits remained significantly higher *($P < 0.01$)* on day 10 and this increase continued *($P < 0.05$)* to day 15. During recovery phase the level of serum ALP decreases and was found non-significant. ALP is highly related to liver; however, kidney impairment also depicts a rise in ALP level. Shalini *et al.* (2013) stated that hepatic dysfunction is associated with clinical use of NSAIDS. Hussain *et al.* (2008) noticed that serum creatinine and urea levels were elevated in four avian species treated with diclofenac sodium. The mechanisms of diclofenac induced hepatic idiosyncratic adverse drug reactions remain largely unknown (Boelsterli 2003). Histological findings showed that administered piroxicam to group B noticed mild dilation of distal convoluted tubules, slight disruption of the proximal convoluted tubules glomerulus was seen to be unchanged, shrinkage of glomerulus with widened bowman's space mild inflammatory cellular infiltration and hyperaemia in intratubular spaces Similar findings are reported by Ahmad *et al.* (2017) that administration of meloxicam Histopathologically alters the and slight dilation of renal tubules in kidneys, kidney sections showed severe shrinkage of glomerulus with widened bowman's space.

Diclofenac related hepatotoxicity may be attributed to three reactive metabolites of diclofenac sodium in the liver, namely 4-hydroxy-3diclofenac, 5-hydroxyl-4diclofenac and 5-hydroxyl-6diclofenac (Daly *et al.* 2007). Both the formation of toxic metabolites and covalent binding of the drug to hepatic proteins have been invoked to explain its toxicity (Julie *et al.* 2015). The alterations found with diclofenac and piroxicam were in agreeance with those found by Burukoglu *et al.* (2016) who reported shrinkage of Bowman's capsule, dilation of distal tubules and vasoconstrictions of arterioles with piroxicam administration. Similar findings were also reported by Ahmad *et al.* (2017) who reported shrinked glomerulus with widened bowman's spaces. Glomerular shrinkage might be due to the higher concentration of piroxicam in the blood which affected capillary constriction resulted in a decreased glomerular filtration rate.

Conclusion

Hence, it is concluded from this study that at similar doses piroxicam exerted less severe changes in the biochemical parameters as compared to diclofenac, which is also revealed in histopathological findings, that marked lesions in renal structure were noted in diclofenac treated group either on day 15 or 30 as compared to piroxicam treated group.

Authors Contributions

All authors contributed equally to study design, sampling, methodology, interpretation of results, and manuscript writing.

Conflict of Interest

The authors declare that there is no conflict of interest for this publication.

Data Availability

Available of data can be shared on demand

Ethics Approvals

Experiments on animals were performed with the guideline of the ethical committee Sindh Agriculture University certificate by a protocol approved No. DAS/381/2016.

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