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Research Article

“Adverse Effects Of Carprofen And Meloxicam In Male Rats”

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ABSTRACT

The present study was conducted to investigate some adverse effects of carprofen and meloxicam in albino male rats on some male reproductive parameters including index weight (testes, epididymis and other accessory genital glands), sperm quality (sperm motility, sperm abnormalities and sperm count) ,some biochemical parameters(ALT,AST, serum creatinine ,serum total protein, albumin, globulin and serum testosterone)) as well as hemogram and histopathological examination of the selected organs. Twenty seven male albino rats of 130-150 gm body weight and 3 months age were divided into 3 groups each of 9 rats. The first group was injected 0.2ml saline i/m once daily for 7 days and served as control group. The second group was injected i/m once daily for 7 days with a carprofen at dose of 5.2mg/kg b.wt. The third group was injected i/m once daily for 7 days meloxicam at dose of 1.2 mg/Kg b.wt. Rats were kept under hygienic measures for 56

days then blood samples was taken and animals were scarified to obtain semen sample for semen analysis and organs for histopathological examination. Results revealed that carprofen and meloxicam exerted an deleterious effects on male fertility as they impaired semen quality manifested by reduced sperm count, motility and increasing the number of abnormal sperm. The testosterone level, index weight of testes, epididymis and other accessory genital glands were significantly decreased. Moreover, both drugs induced, neutropenia and lymphopenia in addition meloxicam induced leucopenia, eosinophilia and monocytopenia. Both drugs induced no changes in liver and kidney functions. It could be concluded that carprofen or meloxicam repeated administration induced deleterious adverse effects on male fertility so they must be used with care to avoid possible fertility troubles especially during breeding season.

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INTRODUCTION:

Non-steroidal anti-inflammatory drugs (NSAIDs) are a bunch of heterogeneous compounds that inhibit one or more substances created throughout inflammatory reactions. NSAIDs are extensively utilized in both human and animals for their analgesic, antipyretic and anti-inflammatory properties (Khan and McLean, 2012). NSAIDs are pharmacologically effective medication in all worlds. These medications are widely used as self-therapy to preclude the disorder pain (Lafoutand Ghasemi, 2018).

The efficiency of newer NSAIDs' anti-inflammatory drugs as carprofen, and meloxicam arises from reversible inhibition of cyclooxygenases with the next property to the cyclooxygenase-2 (Streppa et al., 2002 and Clark et al., 2003) spending improved tolerability with low gastrointestinal and renal toxicity in experimental animal models (Lazzaroni and Porro, 2004 and Patrignani et al., 2011).

Carprofen is a NSAID with characteristic analgesic and antipyretic activity nearly equivalent to indomethacin in animal models. It has a moderate potency to inhibit phospholipase A2 and also is a reversible inhibitor of cyclooxygenases with higher selectivity to the cyclooxygenase-2 (Baruth et al., 1986; Brideau et al., 2001; Streppa et al., 2002 and Clark et al., 2003).

Meloxicam is an enolic acid derivative non-steroidal anti-inflammatory drug, exhibiting property for cyclooxygenase (COX)-2 over COX-1 showing potent anti-inflammatory and analgesic activity along with low gastrointestinal toxicity in animal models. It belongs to a group of COX-2 selective inhibitors anti-inflammatory drugs with a much better safety profile than typical COX-1 and COX-2 nonselective anti-inflammatory drugs. As a result of COX-2 advantageous, it might be expected to have less gastrointestinal toxicity than nonselective NSAIDs. (Vane and Botting, 1996; Ogino et al., 1997 and Ogino et al., 2002).

The mechanism of action of carprofen, like that of alternative NSAIDs, is believed to be related to the inhibition of cyclooxygenase activity. Two distinctive cyclooxygenases have been described in human and animals (Vane and Botting, 1996). COX-1 synthesizes prostaglandins vital for normal gastrointestinal and

renal capacity. The inducible cyclooxygenase, COX-2, produces prostaglandins involved in inflammation. Inhibition of COX-1 is assumed to be related to gastro intestinal and renal toxicity whereas hindrance of COX-2 lead to anti-inflammatory activity. The specificity of a certain NSAID for COX-2 versus COX-1 could vary from species to species (Grossman et al., 1995). Studies were conducted to determine the influence of COX inhibitors on reproduction revealed that the suppression of these enzymes interferes with the androgen production and inflicting sperm maturation defects (Balaji et al., 2008).

Aim of work:

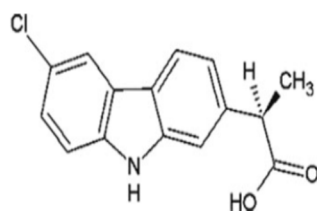
The present work was designed to study the adverse effects of carprofen and meloxicam as anti-inflammatory drugs on fertility, hemogram, some biochemical parameters and histopathological findings in male albino rats.

MATERIALS AND METHODS:

Chemicals

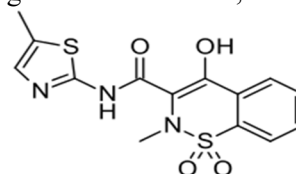
Drugs:

Carporfen (Morprofen[®]) contain carporfen 50mg/ml was obtained from Pharma Swede -Egypt.



Carprofen [(1S)-2-(6-chloro-9H-carbazol-2-yl)propanoic acid]. It was injected intramuscularly at the recommended therapeutic dose (5.2 mg/ kg b.wt.), once daily for 7 days.

Moloxicam (Metacam[®]) was obtained from Boehringer Ingelheim Vetmedica, Inc. Germany.



Molexicam[4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-,1,1-dioxide.] It was injected intramuscularly at the recommended therapeutic dose (1.2mg/kg b.wt.) once daily for 7 days. The rat doses of both drugs were calculated according to Paget and Barnes (1964).

Chemical kits:

Diagnostic kits for hemoglobin, serum enzymes (ALT, AST), total protein, albumin, cholesterol and creatinine were obtained from Diamond chemicals company, Inc. Serum testosterone was determined using an enzyme immunoassay kit immune metrics Ltd., London, UK.

Experimental design:

Twenty-seven mature male albino rats weighting from 130-150 g and approximately 90 day old were used in this study. The animals were kept under hygienic conditions, fed on standard pellets and water ad-libitum. Rats were left two weeks for acclimatization, and then divided into 3 equal groups each of nine.

1-Control group was injected intramuscularly with saline 2 ml /kg b.wt.

2-Carprofen treated group was injected intramuscularly with carprofen (5.2 mg/kg b.wt.) once daily for successive 7 days.

3-Molexicam treated group was injected intramuscularly with meloxicam (1.2 mg/kg b.wt.) once daily for successive 7 days.

Sampling:

Blood samples were collected from the retro-orbital venous plexus from each rat at the end of experiment (after 56 days since beginning of drug administration) under light volatile anesthesia. Blood was divided into two tubes; the first was anticoagulated with EDTA for hematological examination. The second blood sample was gotten in a spotless dry rotator tube, permitted to clot and afterward centrifuged at 3000 rpm for 10 min at 4 °C to separate serum. Sera were deep frozen at - 20 °C until utilized for biochemical tests. Specimens from liver, kidney, testes, epididymis and accessory genital glands were collected and fixed in neutral formalin 10% for histopathological examination.

Reproductive organs index weight:

The animals were sacrificed; the testes, epididymis and accessory sex organs were dissected out, grossly examined and weighed. The index Weight (I.W) of each organ was calculated as described by Matousek (1969).

Index weight (I.W) = organ weight / body weight x 100

Fertility studies:

After scarification of rats, the epididymal content of each rat was taken by sharp cutting of the epididymal tail and squeezed gently on sterile glass watch to estimate the progressive motility, sperm cell count and sperm abnormalities according to the method described by **Bearden and Fuquay (1980)**.

Sperm count

For counting epididymal sperm, a haemocytometer and a pipette of RBCs counting were used. A drop of undiluted caudal epididymal content was withdrawn up to the mark 0.1 and the pipette was then filled up to the mark 101 by sodium bicarbonate 5% solution for breaking up the mucous droplets in the diluting pipette.

Sperm progressive motility and abnormalities:

A clean dry slide was placed on heated stage microscope and allowed to warm at temperature 38 °C. A drop of freshly undiluted semen was placed on this slide, mixed with two drops of saline using glass rod. Uniform mixture must be prepared for accurate determination. The progressively motility percentage were estimated and recorded. Then immediately, two equal drops of Eosin-Nigrosine stain were added to the diluted semen, mixed well and the film was spread on the slide. Three hundred sperm was observed under high power lens and the percentage of abnormal sperms was estimated and recorded.

Hormonal assay: Serum testosterone was determined using an enzyme immunoassay according to Demetrius (1987).

Hematological studies:

Hemoglobin concentration, packed cell volume, erythrocytic and total leukocytic counts and differential leucocytic count was determined according to Feldman et al., (2000).

Serum biochemical assays:

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were measured calorimetrically according to Reitman and Frankel (1957). Serum creatinine was measured by colorimetric method according to Houot (1985). Serum total protein was measured using colorimetric method as described by Doumas et al., (1971). Serum albumin was determined according to Doumas and Biggs (1972). Serum globulin level was determined by subtracting the albumin value from total protein value of the same sample as described by Coles (1974).

Histopathological examination:

Fresh specimens from liver, kidney, testes, epididymis and accessory genital glands were removed and preserved in 10% buffered formalin solution and histopathological examination is done according to Bancroft et al., 1996.

Statistical Analysis:

Statistical analysis was performed using the IBM SPSS Statistics V20.0.0 documentation software (2011). The data were analyzed using analysis of variance (One-way ANOVA). All data were expressed as the mean \pm standard error (SE).

RESULTS:

Male rats were administered carprofen (5.2 mg/kg b.wt.) or meloxicam (1.2 mg/kg b.wt) intramuscularly once daily for 7 days and scarified after 56days post injection showed the following results:-

Reproductive organs index weight:

It was found that intramuscular administration of carprofen (5.2 mg/kg b.wt.) or meloxicam (1.2 mg/kg b.wt.) once daily for 7 consecutive days in male albino rats induced a significant ($P \leq 0.05$) reduction in index weight of testes, epididymis, prostate glands and seminal vesicle as well as serum free testosterone hormone level after 56 days in both treated groups as compared with control group (table 1).

Semen picture studies: (sperm count, sperm motility% and sperm abnormalities): There were significant ($P \leq 0.05$) decrease in the sperm count and progressive sperm motility % as well as a significant ($P \leq 0.05$) increase in sperm

abnormalities after 56 days in both treated groups as compared with control group (table 2).

Hemogram studies:

There were insignificant changes in haemoglobin concentration, packed cell volume, RBCs count. On the other hand i.m. administration of carprofen (5.2 mg/kg b.wt) in rats showed non-significant decrease in total leucocytic count with significantly apopenia and neutropenia when compared to control group. Meloxicam (1.2 mg/kg b.wt) induced leukopenia accompanied with lymphopenia and neutropenia as well as monocytopenia but significant ($P \leq 0.05$) increase in eosinophils count as compared to control group (table 3).

Biochemical studies:

There were insignificant changes in serum ALT, AST, and creatinine in both treated groups as compared to control group (table 4). Also, non-significant changes in serum total protein, albumin, and globulin levels and cholesterol as compared to control group (table 5).

Histopathological findings:***Carprofen treated rats:***

The testes showing degenerated tubules and lumens contain little sperms. (Fig. 1) while the epididymis showed normal histological appearance of their tubules. (Fig. 2). The prostate gland showing mild acinar dilatation of some acini with little amount of secretion. (Fig. 3). The seminal vesicles showing cystic dilatation and hyper proliferation. (Fig.4). The liver showing mild changes such as Congestion and widening of hepatic sinusoids (Fig.5). kidney showing congestion. (Fig. 6)

Meloxicam treated rats:

The testes of meloxicam treated rats revealed degenerated seminiferous tubules, lumen contain little sperms and congestion of interstitial blood vessels. (Fig. 7). The epididymis showing little sperms in lumen and congestion of interstitial blood vessels. (Fig. 8). The prostate gland showing mild acinar dilatation some acini has little amount of secretion. (Fig. 9). The seminal vesicles showing cystic dilatation and hyper proliferation. (Fig. 10). The liver showing congestion and widening of hepatic sinusoids. (Fig. 11). The kidneys showing

more congestion of interstitial blood vessels compared to carprofen treated rats. (Fig. 12).

Table (1) : Effect of Carprofen (5.2 mg/kg b.wt.) and Meloxicam (1.2 mg/kg b.wt.) on Index weight of testes, epididymis and accessory genital glands as well as testosterone hormone level.

Parameters	Groups		
	Control	Carprofen	Meloxicam
Index weight of testes	0.84±0.07 ^a	0.61± 0.02 ^c	0.62±0.03 ^b
Index weight of epididymis	0.30±0.02 ^a	0.23± 0.01 ^b	0.22±0.02 ^b
Index weight of prostate glands	0.31±0.02 ^a	0.22± 0.02 ^b	0.213±0.01 ^b
Index weight of seminal vesicle	0.59±0.03 ^a	0.48±0.02 ^b	0.46±0.03 ^b
Testosterone hormone level (ng/ml)	6.93±0.57 ^a	3.18±0.72 ^b	4.19±0.94 ^b

All values are expressed as mean ± S.E. Number of rats in each group is nine. Values with different letters at the same row are significantly different at $P \leq 0.05$ (one way ANOVA test).

Table (2): Effect of carprofen (5.2 mg/kg b.wt.) and meloxicam (1.2mg/kg b.wt.) intramuscular administration once daily for 7 consecutive days on some fertility parameters in male albino rats.

Parameters	Groups		
	Control	Carprofen	Meloxicam
Sperm cell concentration (10^6 / ml)	25.27±0.99 ^a	18.20±0.37 ^b	17.59±2.20 ^c
Sperm motility (%)	95.33±0.53 ^a	45.89±1.59 ^b	62.44±1.51 ^b
Sperm abnormalities (%)	8.73±0.31 ^a	22.33±0.93 ^b	13.37±0.41 ^b
Sperm live (%)	95.33±0.47 ^a	47.44±2.55 ^b	62.67±2.24 ^b

All values are expressed as mean ± S.E. Number of rats in each group is nine. Values with different letters at the same row are significantly different at $P \leq 0.05$ (one way ANOVA test).

Table (3): Effect of carprofen (5.2 mg/kg b.wt.) and meloxicam (1.2 mg/kg b.wt.) on hemogram.

Parameter		Group		
		Control	Carprofen	Meloxicam
Hb concentration (g/dl)		14.64± 0.29 ^a	14.65± 0.33 ^a	14.41± 0.24 ^a
PCV (%)		50.56±0.18 ^a	50.22±0.36 ^a	49.78±0.47 ^a
RBCs count ($\times 10^6$ / ul)		8.27 ±0.08 ^a	8.13 ± 0.16 ^a	8.17 ± 0.04 ^a
WBCs count ($\times 10^3$ / ul)		7.28 ± 0.67 ^a	6.02±0.47 ^a	5.26±0.61 ^b
Differential count	Lymphocyte ($\times 10^3$)	0.035±0.003 ^a	0.29±0.002 ^b	0.21±0.005 ^b
	Neutrophils (x 10^3)	0.1 ± 0.003 ^a	0.07 ± 0.005 ^b	0.06 ± 0.005 ^b
	Basophile ($\times 10^3$)	0.001± 0.0001 ^a	0.002 ± 0.0005 ^a	0.001±0.0001 ^a
	Eosinophil (x 10^3)	0.002±0.0001 ^a	0.002±0.0001 ^a	0.004 ± 0.0002 ^b
	Monocyte (x 10^3)	0.01±0.0003 ^a	0.01±0.0003 ^a	0.004 ± 0.0001 ^b

All values are expressed as mean ± S.E. Number of rats in each group is nine. Values with different letters at the same row are significantly different at $P \leq 0.05$ (one-way ANOVA test).

Table (4): Effect of carprofen (5.2 mg/kg b.wt.) and meloxicam (1.2 mg/kg b.wt.) on some liver and kidney function tests.

Parameters	Groups		
	Control	Carprofen	Meloxicam
Serum ALT activity (U/L)	63.33±3.45 ^a	63.75±1.80 ^a	64.00±2.69 ^a
Serum AST activity (U/L)	164.44±13.19 ^a	173.44±4.14 ^a	165.22±14.53 ^a
Serum creatinine level (mg / dl)	1.34±0.11 ^a	1.38±0.05 ^a	1.16±0.09 ^a

All values are expressed as mean ± S.E. Number of rats in each group is nine. Values with different letters at the same row are significantly different at $P \leq 0.05$ (one-way ANOVA test).

Table (5): Effect of carprofen (5.2mg/kg b.wt.) and meloxicam (1.2mg/kg b.wt.) on serum total protein, albumin and globulin levels.

Parameters	Groups		
	Control	Carprofen	Meloxicam
Serum total protein level (g /dl)	6.85±0.11 ^a	6.90±0.24 ^a	7.34±0.17 ^a
Serum albumin level (g / dl)	3.81±0.09 ^a	3.91±0.17 ^a	3.85 ±0.16 ^a
Serum globulin level (g / dl)	3.11±0.17 ^a	3.15±0.15 ^a	3.62±0.24 ^a
Cholesterol	106.31±4.61 ^a	98.11±4.19 ^a	101.50±2.75 ^a

All values are expressed as mean ± S.E. Number of rats in each group is nine. Values with different letters at the same row are significantly different at $P \leq 0.05$ one-way ANOVA test).

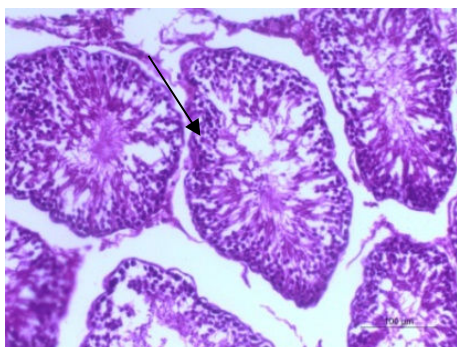


Fig. (1): Testis of male rats administered therapeutic dose (5.2 mg/ kg b.wt.) of carprofen and scarified 56 days post administration showing degenerated tubules and lumen contain little sperms. H&E stain x 100.

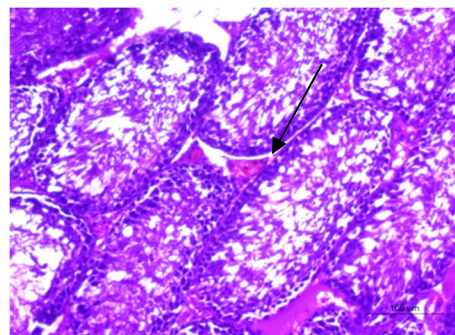


Fig. (7): Testis of male rats administered therapeutic dose (1.2mg/ kg b.wt.) of meloxicam and scarified 56 days post administration showing degenerated seminiferous tubules, lumen contain little sperms and congestion of interstitial Bvs. H&E stain x 100.

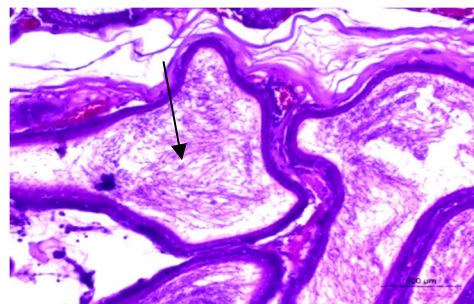
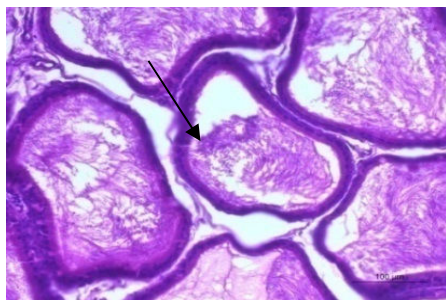


Fig. (2): Epididymis of male rats administered therapeutic dose (5.2mg/ kg b.wt.) of carprofen and scarified 56 days post administration showing normal findings. H&E stain x 100.

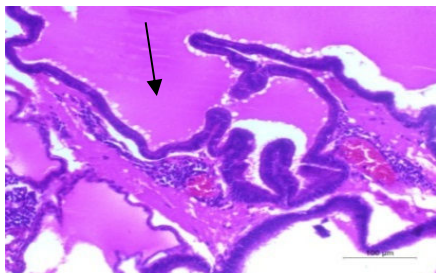


Fig. (8): Epididymis of male rats administered therapeutic dose (1.2mg/ kg b.wt.) of meloxicam and scarified 56 days post administration showing little sperms in lumen and congestion of interstitial Bvs H&E stain x 100.

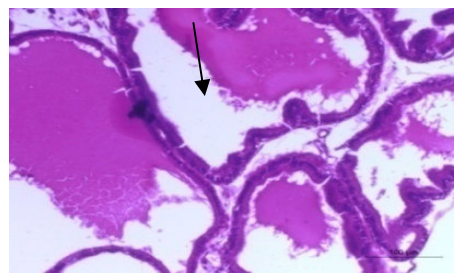


Fig. (3): Prostate of male rats administered therapeutic dose (5.2 mg/ kg b.wt.) of carprofen and scarified 56 days post administration showing mild acinar dilatation and some acini has little amount of secretion. H&E stain x 100

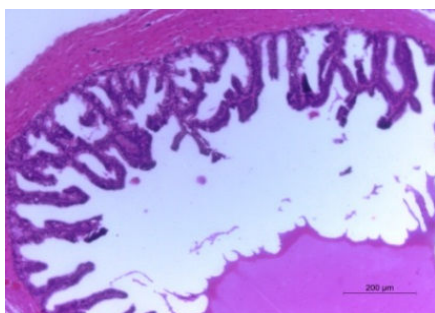
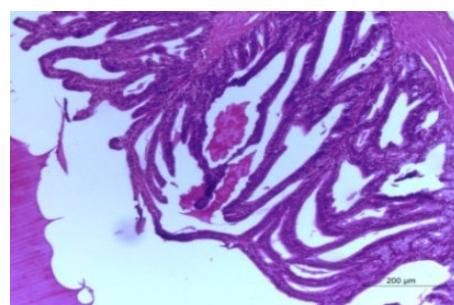


Fig. (9): Prostate of male rats administered therapeutic dose (1.2mg/ kg b.wt.) of meloxicam and scarified 56 days post administration showing mild acinar dilatation some acini has little amount of secretion. H&E stain x 100



Fig(4): Seminal vesicle of male rats administered therapeutic dose (5.2mg/ kg b.wt.) of carprofen and scarified 56 days post administration showing cystic dilatation and hyperproliferation. H&E stain x 100.

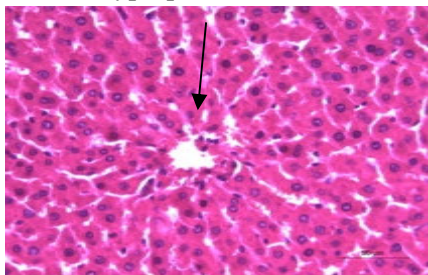


Fig. (10): Seminal vesicle of male rats administered therapeutic dose (1.2mg/ kg b.wt.) of meloxicam and scarified 56 days post administration showing cystic dilatation and hyperproliferation. H&E stain x 100.

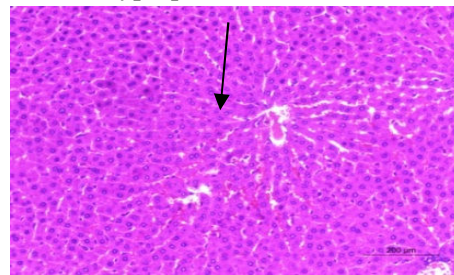


Fig. (5): Liver of male rats administered therapeutic dose (5.2 mg/ kg b.wt.) of carprofen and scarified 56 days post administration showing congestion, widening of hepatic sinusoids and leucocytic infiltration in hepatic parenchyma. H&E stain x 100.

Fig. (11): Liver of male rats administered therapeutic dose (1.2mg/ kg b.wt.) of meloxicam and scarified 56 days post administration showing Congestion and widening of hepatic sinusoids H&E stain x 100.

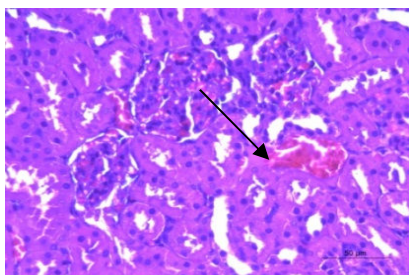


Fig (6): Kidney of male rats administered therapeutic dose (5.2 mg/ kg b.wt.) of carprofen and scarified 56 days post administration showing congestion. H&E stain x 100.

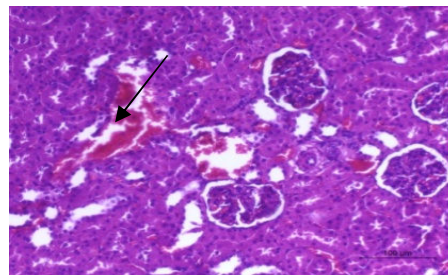


Fig. (12): Kidney of male rats administered therapeutic dose (1.2mg/ kg b.wt.) of meloxicam and scarified 56 days post administration showing more congestion of interstitial Bvs. H&E stain x 100.

Histopathological Findings Of Carprofen And Meloxicam Treated Rats

DISCUSSION

Non-steroidal anti-inflammatory drugs (NSAIDs) as meloxicam and carprofen are commonly used for treatment of osteoarthritis and other acute or chronic conditions associated with inflammation and pain in human and animals but they may have some deleterious effects on fertility (Basha et al., 2011). The duration of the experimental period was 56 days to span a complete spermatogenic cycle in male rats which is ranged from 48 –56 days for accurate evaluation of these drugs effects on male fertility (Clermont and Harvey, 1965).

The meloxicam and carprofen administration to male rats caused significant reduction in index weights of testes, epididymis, prostate glands and seminal vesicle. This reduction can be explained on basis of our findings of decreased free serum testosterone level. Our findings are compatible with those recorded by (Zaied, 2004 and El-Nakeeb et al., 2011) they mentioned that administration of meloxicam or tolfenamic acid induced significant decrease in the weight of testes, epididymis and accessory sex glands in male rats and attributed this effect to the direct impact of meloxicam and carprofen on gonadal tissue (Leydig cells) or due to the inhibitory effect on between hypothalamus pituitary testes axis. The decrease in weight of the sex organs may be due to reduction in testosterone hormone level, as weights of prostate and seminal

vesicle and maintenance of their secretions is androgen dependent and may reflect changes in the endocrine status or testicular function (Srikhanth et al., 1999 and Ono et al., 2004).

Our study revealed that meloxicam and carprofen administration significantly impaired semen quality which is clarified by significant decrease in sperm count, motility and alive sperm percent with increased sperms abnormalities percentage. These findings are supported by the histopathological picture including degenerative changes of seminiferous tubules as well as other accessory genital organs. The result of impaired sperm quality may be explained on basis of COX-₂ suppression by these drugs lowers sperm motility and can interfere with sperm capacitation which is essential for fertilization. COX-₂ is constitutively expressed in testes and its suppression interferes with the testosterone production, causing sperm maturation defects (Balaji et al., 2008 and Uzun et al., 2015). Also low prostaglandin levels have been associated with reduced sperm quality, motility and penetration capacity, (Boughton-Smith and Whittle, 1983; Ricciotti and FitzGerald, 2011) and fertility (Nelson, 2005). The negative effects of low levels of seminal prostaglandins on sperm concentration and motility might be correlated respectively with decreased adenylyl cyclase and testicular androgen activity. (Isidori et al., 1980). Moreover, the lower

testosterone level in rats treated with meloxicam and carprofen may be attributed to the degenerative changes in testicular tissue in addition to their inhibitory effect on gonadotrophic hormone that is accountable for testosterone secretion. (Amiridis et al., 2009). The Leydig cells produce PGD2 which plays a stimulatory role in the basal production of testosterone (Schell et al., 2007). The basic anti-inflammatory mechanism of meloxicam and carprofen is through inhibition of prostaglandin synthesis which may affect testosterone level. Thus, the deleterious effect on spermatogenesis may be attributed to the reduction in serum testosterone levels as testosterone is essential to maintain the structure and function of the male accessory sex gland and lack of testosterone disrupts spermatogenesis that does not proceed beyond the meiosis stage (Broock for and Blake, 1997 and Walker, 2011).

Concerning our results of hemogram, there were no significant changes in erythrogram after carprofen and meloxicam administration. our results are compatible with records of in significant changes of RBCs, PCV% after meloxicam administration in African grey parrots (Montesinos et al., 2015) and rats (Amin et al., 2017 and El-sayed et al., 2017). The present findings of leukopenia and monocytopenia in meloxicam treated group in addition to lymphopenia and neutropenia in both carprofen and meloxicam treated groups these findings may be due to their effect on bone marrow granulopoiesis, these results agreed with Smith, 1989 who reported that leukopenia and thrombocytopenia may accompanied NSAID administration. The present neutropenia finding is compatible with reports of Strom et al., 1993 and van der Klauw et al., 1999 that NSAIDs have been associated with significantly elevated risks of neutropenia in all epidemiological studies, and also with record of Al-Rekabi et al., 2009, who registered significant neutropenia in meloxicam treated rats. Eosinophilia in meloxicam treated rats are consistent with findings of Smith, 1989 who reported that NSAIDs may cause hematologic side effects such as eosinophilia, granulocytopenia and leukopenia. The eosinophilia may occur due to delayed reactions to

NSAIDs mediated by drug-specific cytotoxic T cells through type IV allergic reactions (Pichler, 2003).

The non-significant changes in serum ALT, AST, total protein, albumin, globulin, cholesterol, and creatinine levels in both carprofen and meloxicam treated rats as compared to control group are compatible with our findings of normal histopathological changes in liver and kidney except as congestion. Our results are compatible with records of non-significant changes in total plasma protein and creatinine in blood of carprofen treated cats (Steagall et al., 2009) and with report that chronic COX-2 inhibitors administration did not show observational or toxicological effects on the blood biochemistry (Wang et al., 2018.)

CONCLUSION

We could be concluded that carprofen or meloxicam repeated administration induced deleterious adverse effects on male fertility including impaired semen quality as well as varying degrees of degenerative changes of testes and accessory genital glands, so they must be used with care to avoid possible fertility troubles especially during breeding season.

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