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The Effect Ofmeloxicam and Piroxicamon the Fertility of Male Rats

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Abstract: *Meloxicam and piroxicam are used as anti-steroidal anti-inflammatory agents in the treatment of arthritis, rheumatoid, acute and chronic pain in humans and animals, and are often accompanied by some side effects such as gastrointestinal disorders and urinary tract diseases. This study aimed to know the side effects of these drugs on fertility in male rats as a model for the effects that may arise in humans and animals.*
This laboratory study was conducted on 60 male white rats with a weight of 170-180 g. At the end of the injection of drugs one day, 2 weeks, 4 weeks and 8 weeks, five rats were taken from each group and slaughtered and the blood was taken in centrifuge tubes to prepare the serum for the hormone measurements (FSH, LH, Prolactin, Free and direct testosterone) preserved at -20 ° C until the measurements were performed. The rats were then dissected to extract the testis and the follicle and seminal vesicles and weighed with a sensitive balance to calculate the index weights for these organs. The study of histopathology on these organs had been conducted with sperm samples from the epididymis to study the seminal fluid (spasmodic movement, individual sperm movement, total number, percentage of living to dead sperms), as well as deformities that occurred in some sperm.The study concludes that giving meloxicam &piroxicam to male rats for 7 days has had negative effects on the level of reproductive hormones, weight of the genitals and sperm image, as well as the histopathological picture of the genitals, which makes us advised not to use these drugs in male animals.
Key words: *Fertility, meloxicam, piroxicam, NSAID, Sterility*

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I. Introduction

The most prominent members of NSAIDS are aspirin, ibuprofen and naproxen, are all available over the counter in most countries. Paracetamol(acetaminophen) is generally not considered an NSAID because it has only little anti-inflammatory activity. It treats pain mainly by blocking COX-2 mostly in the central nervous system, but not much in the rest of the body.*(Warden,2010).*NSAIDs inhibit the activity of both cyclo-oxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and thereby, the synthesis of prostaglandins and thromboxanes. It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers. ***(Hinz ,2008)***. The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly prevalent. Use of NSAIDs increases risk of having a range of gastrointestinal (GI) problems. When NSAIDs are used for pain management after surgery they cause increased risk of kidney problems ***(Michael J. Curtis,1998).***An estimated 10-20% of NSAID patients experience dyspepsia. In the 1990s high doses of prescription NSAIDs were associated with serious upper gastrointestinal adverse events, including bleeding. Over the past decade, deaths associated with gastric bleeding have declined. NSAIDs, like all drugs, may interact with other medications. For example, concurrent use of NSAIDs and quinolonesmay increase the risk of quinolones' adverse central nervous system effects, including seizure ***(Rostom etal.,2002)***

Human semen is the richest known source of prostaglandins (PGs) in vertebrates. However, in contrast to the enormous amount of research which has been carried out on the pharmacological effect and physiological roles of PGs in the female, research into the function of PGs in semen has remained at a comparatively low level despite the absence of any convincing explanation for the presence of these compounds in semen at such large concentrations, ***(Cenedella, 1975).***Marley and Smith reported that treatment of male mice for 7 days with high doses of indomethacin reduced the fertility of the animals, but it was not clear whether this antifertility effect was related to the measured decrease in seminal PGs or to unspecific effects of the treatment on sexual drive. ***(Marley and Smith ,1974)***.

In the present study, the effect of prolonged administration of various non-steroidal anti-inflammatory drugs on male fertility was studied in rats. To reach and maintain drug concentrations similar to those occurring during anti-inflammatory therapy in humans, the pharmacokinetics of the drugs in male rats were determined

before the fertility experiment and were taken into account for dose regimens. The efficacy of the treatments with respect to inhibition of PG synthesis was determined by analysis of concentrations of PGE-2 in seminal fluid.

1. METHOD:

Sixty mature male Albino rats weighing from 170-180 gm each of 4-5 month age were used in this study.The animals were divided randomly into 3 equal groups as following:Group 1:kept as control for the groups(2 and 3),it contains 20 rats injected I/M with 0.4 ml saline once daily for a week.Group 2:it were injected I/M once daily for a week with therapeutic dose of feldene(0.18 mg/100gm B.Wt).Group 3:it were injected I/M meloxicam once daily for 7 days in a dose of (0.135 mg/100gm B.Wt).At the end of 1^{st}-2^{nd}-4^{th} and 8^{th} week post each drug administration, blood samples were collected in test tubes from five rats from each group.

Blood samples were collected without anticoagulant at 1 day,2,4 and 8weeks post drug administration to obtain serum after centrifugation of the clotted blood sample for 15 min at 3000 r.p.m to estimate FSH,LH and testosterone.

1.1Effect on sex organs weight index:

The animals were then immediately sacrificed and the testes,seminal vesicles and prostate glands were dissected out,and were weighed every time.After separation of epidedymis from testes,it was transferred into petridish and then evacuated into a petridish containing normal saline***(Bearden and fluquany,1980).***The semen sample was examined for:

1.2Mass motility:

A dry and clean slide was prepared and then a drop of collected semen was placed and then examined under microscope.

1.3 individual motility:

Another drop of semen was put on a dry and clean slide and covered by dry and clean cover slide and examined under microscope.

1.4 Determination of percent of live,dead and abnormal sperm:

A drop of semen is placed on a dry and clean slide then adrop of eosin stain are added and mixed and then left to dry at room temperature and then examined under microscope to determine live, dead and abnormal sperm***.(Hancock,1951).***

1.5 sperm count:

A drop of semen was placed on a dry and clean hemocytometer and then covered by a dry and clean cover slide then examined under microscope to determine sperm count by using sperm counter. **(**Hemocytometer was washed first by normal saline and then left to dry at room temperature. The spermatozoa were counted using the high power objective lenses).

1.6Testesterone,FSH,LH assay:

After blood sample collection,serum was collected from each tube and put in Eppendorf for testosterone, FSH and LH.

a-Determination of serum assaying testosterone:

Serum testosterone level was determined by Enzyme Linked Immunosorbent Assay (ELISA) as described by ***Joshi et al,(1979)*** using a diagnostic kit (Immulite/Immulite 1000 testesterone) supplied by Siemens Solution Diagnostics Limited,USA and the Immulite 1000 Analyser.

b- Determination of serum FSH:

Serum FSH level was determined by Enzyme Linked Immunosorbent Assay (ELISA) as described by ***Pierce and Parson (1981)*** and ***Levine et al,(1985)*** using a diagnostic kit (Immulite/Immulite 1000 L.H.) SUPPLIED BY Siemens Solution Diagnostics Limited,USA and the Immulite 1000 Analyser.

1.7 Histopathological changes:

Samples from testicles,seminal vesicles and prostate were collected and kept in 10% formaline solution to be used for histopathological study***.(Bancroft et al.(1996).***

1.8 Statistical Analysis:

Data were collected , arranged and reported as mean ± standard error of mean (Mean+-S.E) of 3 groups (Each group was considered as one experimental unit),summarized and then analyzed using the computer program SPSS (Version 15.0) the statistical analysis was one way analyzes of variance ANOVA test (F-test) and if significant difference between means were found ,Duncaris multiple range test (Whose significant level was defined as ($p>0.05$) was used according to estimate the effect of different treated groups according to ***Sendecor and Cochran,(1982)***.

II. Results

2.1 Effect on sex organs weight index:

The index weight of testicles, seminal vesicle and prostate gland of male rats treated with meloxicam (0.13 mg/100 gm. b.wt.) or piroxicam (0.18 mg/100 gm. b.wt.) for successive 7 days showed significant decrease ($P<0.05$) along the entire course of the study except with the index weight of prostate of meloxicam treated group and testicle and seminal vesicle of the piroxicam treated group after 1st day post end of treatment which showed non-significant changes. Table (1) and Fig. (5, 6 and 7).

Table 1: Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on Index weight of testicle, seminal vesicle (S.vesicle) and prostate gland of male rats.(Mean± S.E.) (n=5)

Group	**Values of weight index of testicles after**			
	1st day	2nd WeeKs	4th Weeks	8th Weeks
Control	o.01±0.000001	0.0155±0.000004	0.0016±0.000002	0.0122±0.000003
Meloxicam	0.0126±0.000002	0.0135±0.000004	0.0012±0.000003	0.0042±0.000003*
Piroxicam	0.0141±0.000001	0.011±0.000006*	0.0117±0.000002*	0.0075±0.000002*
Group	**Values of weight index of prostate gland after**			
	1st day	2nd WeeKs	4th Weeks	8th Weeks
Control	0.0012±0.000002	0.0018±0.000005	0.0015±0.000002	0.0185±0.00002
Meloxicam	0.005±0.000002	0.002±0.000006	0.0018±0.000003	0.0006±0.000001*
Piroxicam	0.0011±0.000002	0.0052±0.000006*	0.0019±0.000002*	0.0016±0.000002*
Group	**Values of weight index of seminal vesicles after**			
	1st day	2nd WeeKs	4th Weeks	8th Weeks
Control	0.0022±0.000002	0.0035±0.000006	0.0013±0.000003	0.00415±0.00001
Meloxicam	0.005±0.000003	0.0051±0.000004	0.0018±0.000002	0.00185±0.000002*
Piroxicam	0.0022±0.000001	0.0013±0.000002*	0.0048±0.000002*	0.0045±0.000002*

*** P < 0.05.**

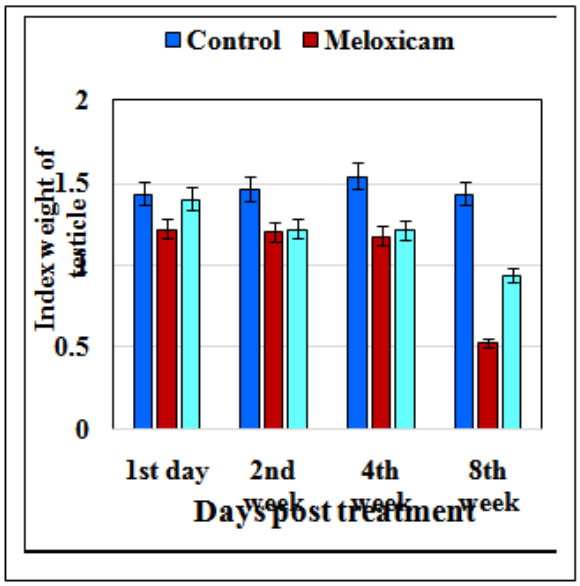


Figure (1): Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on **Index weight of testicle** of male rats.

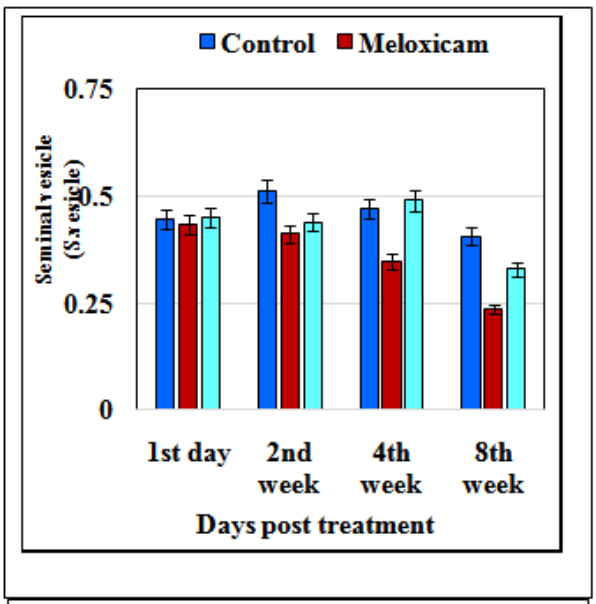


Figure (2): Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on Index weight seminal vesicle of male rats.

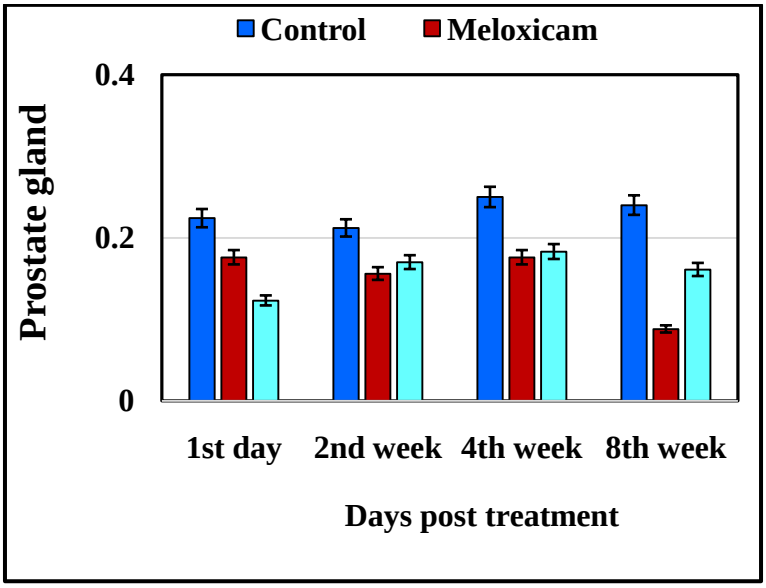


Figure (3): Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on Index weight of prostate gland of male rats.

2.2 Effect on semen picture:

2.2.1: Mass motility

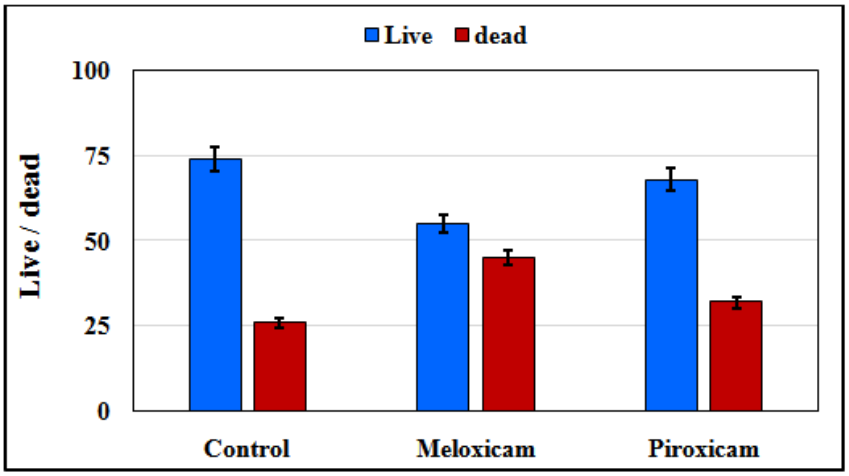
Table 2 showed that mass motility of the meloxicam treated group was medium and that of the piroxicam group was good compared with that of the control group where the mass motility was very good at 8 week post drugs administration.

Table (2): Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on **Semen picture** of male rats. (Mean± S.E.), (n=5)

Groups	**Semen analysis after 8 weeks**				
	Mass motility	**Live / dead**		**Ind. motility**	**Sperm Count.X10^{-6}**
		Live	**dead**		
Control	Very good	74±2.6	26±1.4	96±4.2	120±6.2
Medoxican	Medium	55±2.2*	45±3.2*	82 ±3.6*	81 ± 4.2*
Piroxcam	Good	68±3.2*	32±1.6*	83 ±2.4*	92 ±4.2*

2.2.2: Live/dead percent

It was obvious from Table 2 and Fig 4 that treatment of mature male rats with either meloxicam or piroxicam for 7 successive days afforded a significant decrease ($p<0.05$) in the live/ dead percent compared with the control group on 8th week post drugs administration with meloxicam the most potent inhibitor.



Figure(4): Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on **Semen picture** of male rats (live/dead).

2.2.3 Effect on Individual motility

The individual sperm motility was significantly decreased (P<05) after 8 weeks, post drugs administration compared with control group with meloxicam the most potent inhibitor (Table 6 and Fig 5).

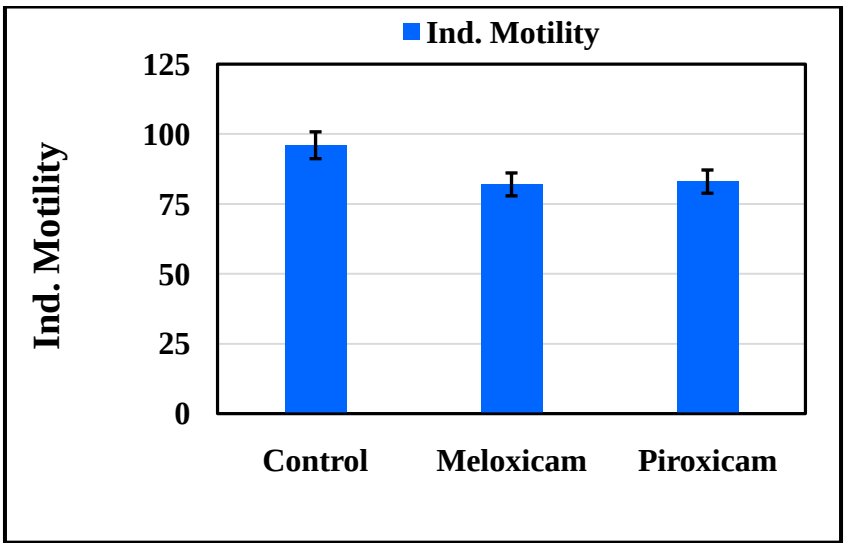


Figure 5: Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on Semen picture of male rats. (Ind.Motility)

2.2.4 Effect on sperm cell count

The sperm cell count was significantly decreased (P < 0.05) after 8 weeks post administration of each drug for successive 7 days compared with control group (Table 6 and Fig 6).

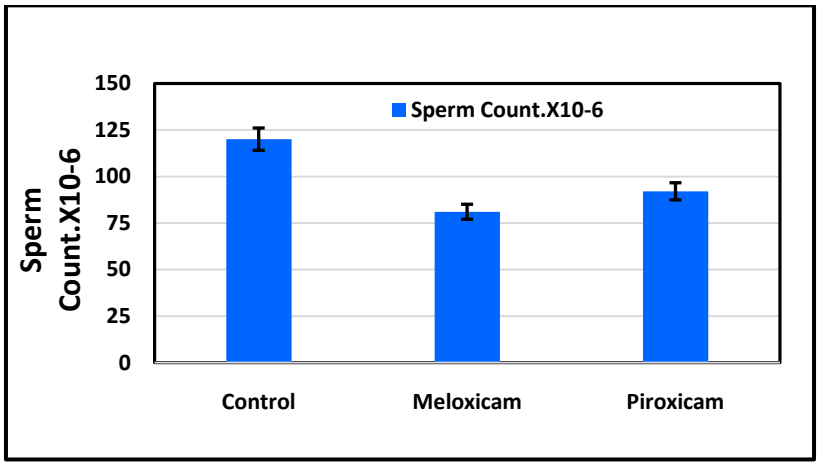


Fig 6: Effect of meloxicam, (0.13 mg/100 gm. b.wt.) piroxicam (0.18 mg/100gm. b.wt.) given I.M for successive 7 days on Semen picture of male rats.(Sperm.count)

2.2.5Effect on sperm abnormality:

The sperm cells of the control group showed normal appearance with very few sperms sowing forked tail and large head. While the sperm cells of the group treated with meloxicam daily for 7 successive days showed many primary abnormalities including double head, broken tail and long head. Whereas, those of the group treated with piroxicam showed also primary abnormality represented by Zegzag shaped tail.

2.3Effect on serum LH:

Table (3) and (Fig. 7) demonstrates that the I. M injection of meloxicam in a dose of 0.135 mg/100gm. b. wt, prioxicam (0.18 mg/100gm) daily for 7 successive days to mature male rats afforded a significant decrease in serm L. H level after 1st day, 2nd, 4th and 8th week post drugs administration compared with control group.

Table (3): Effect of meloxicam, (0.13 mg/100 gm) b.wt. piroxicam (0.18 mg/100gm) given I.M for successive 7 days on **L.H** level of male rats. (Mean± S.E.) (n=5)

Group	Values of L. H in MIU/ml After			
	1st day	2nd week	4th week	8th week
Control	1.12 ±0.04	1.08 ± 0.03	1.15±0.04	1.1± 0.032
Meloxicam	0.62±0.012*	0.56±0.008*	0.66±0.1*	0.72±0.12*
Piroxicam	0.7 ± 0.015*	0.72±0.009*	0.6±0.012*	0.64±0.007*

* P < 0.05.

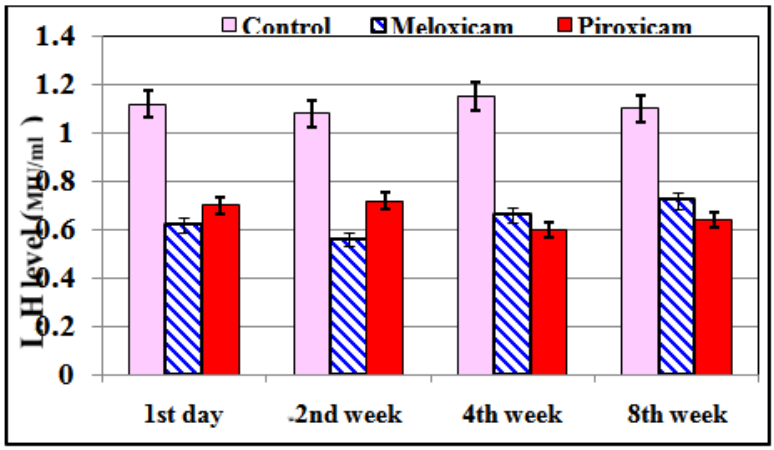


Fig 7: Effect of meloxicam, (0.13 mg/100 gm) b.wt. piroxicam (0.18 mg/100gm) given I.M for successive 7 days on L.H level of male rats.

2.4Effect on serum FSH:

It was clearly evident from table (4) and (Fig., 8) that the I. M injection of the test drugs in their recommended doses and periods elicited a significant decrease in serm FSH level along the entire period of the study compared with control group.

Table (4): Effect of meloxicam, (0.13 mg/100 gmb.wt.) piroxicam (0.18 mg/100gm b.wt.) given I.M for successive 7 days **F.S.H.** level of male rats. (Mean± S.E.) (n=5)

Group	Values of F. S. H in MIU/ml After			
	1st day	2nd week	4th week	8th week
Control	0.21±0.003	0.216 ±0.01	0.22 ±0.014	0.23± 0.018
Meloxicam	0.16±0.004*	0.15±0.0002*	0.17±0.001*	0.165±0.0002*
Piroxicam	0.17±0.0003*	0.18±0.0002*	0.165±0.0003*	0.16 ± 0.0002*

* P < 0.05.

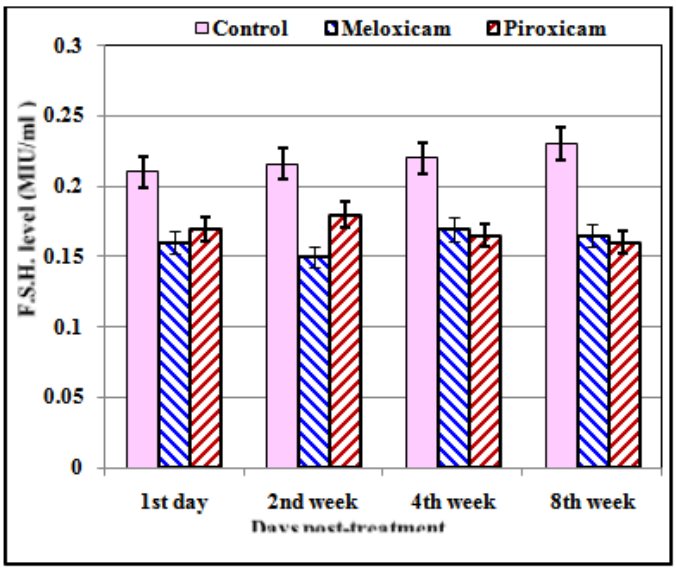


Fig 8: Effect of meloxicam, (0.13 mg/100 gmb.wt.) piroxicam (0.18 mg/100gm b.wt.) given I.M for successive 7 days **F.S.H.** level of male rats

2.5 Effect on serum free and total testosterone level:

Serum free and total testosterone hormone levels were significantly decreased (P<0.05) in response to injection of either meloxicam or piroxicam in their recommended doses and period compared with control group (Table 5 & Fig 9).

Table 5: Effect of meloxicam, (0.13 mg/100 gmb.wt.) piroxicam (0.18 mg/100gm b.wt.) given I.M for successive 7 days on serum **free and total testosterone** level of male rats. (Mean± S.E.) (n=5)

Group	Values of Testosterone in ng/ml After							
	1st day		2nd week		4th week		8th week	
	Free	**Total**	**Free**	**Total**	**Free**	**Total**	**Free**	**Total**
Control	62 ± 1.66	20.42±0.18	63.1±1.1	21±0.12	63.4±2.2	22±1.2	62.6±3.4	22.3±1.02
Meloxicam	36.0±0.3*	14.6 ±0.2*	34.2±1.68*	14.1±0.8*	32± 1.66*	15.2±1.02*	35±3.1*	12±0.66*
Piroxicam	42 ± 2.12*	14.3 ±0.8*	44.2 ± 2.3*	13.6±1.1*	45 ± 3.4*	13.8 ± 1.1*	46 ±2.6*	14.1±0.8*

* P < 0.05.

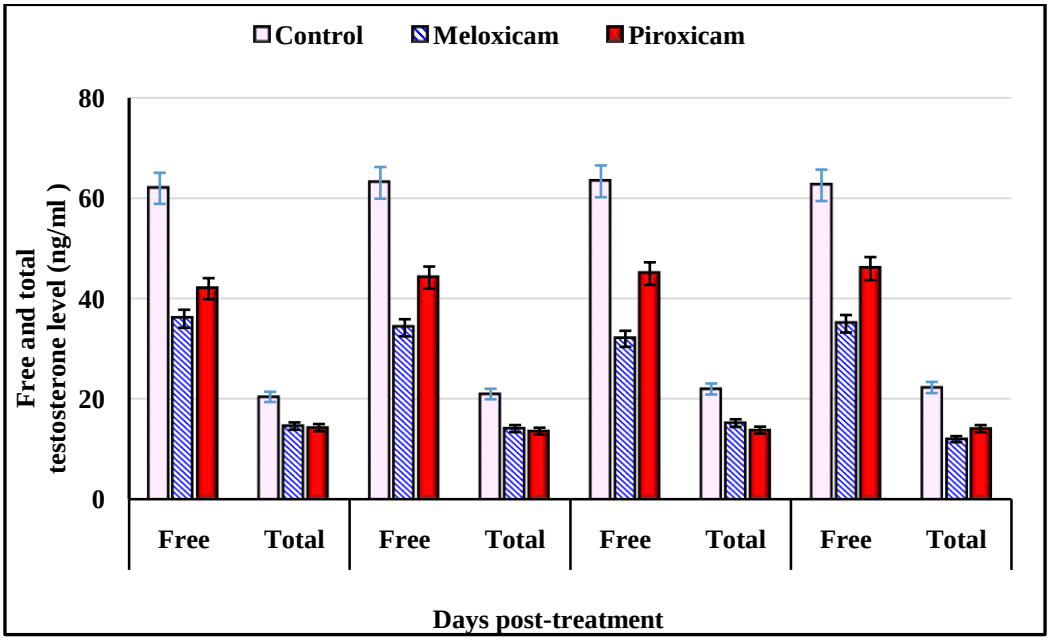


Fig 9: Effect of meloxicam, (0.13 mg/100 gmb.wt.) piroxicam (0.18 mg/100gm b.wt.) given I.M for successive 7 days on serum **free and total testosterone** level of male rats.

2.6 Effect on serum prolactin:

The serum prolactin hormone level was significantly decreased (P<0.05) along the entire course of the study in response to the I. M injection of meloxicam, prioxicam in their recommeded doses and periods compared with control group (Table 6 & Fig 10).

Table 6: Effect of meloxicam, (0.13 mg/100 gmb.wt.) piroxicam (0.18 mg/100gm b.wt.) given I.M for successive 7 days on serum **prolactin** level of male rats. (Mean± S.E.) (n=5)

Group	Values of Prolactin in ng/ml After			
	1st day	2nd week	4th week	8th week
Control	0.4 ± 0.002	0.4 ± 0.0022	0.415 ± 0.03	0.405 ± 0.006
Meloxicam	0.3 ± 0.0022*	0.32 ± 0.0011*	0.312 ± 0.0012*	0.33 ± 0.003*
Piroxicam	0.32 ± 0.006*	0.33 ± 0.008*	0.336 ± 0.004*	0.35 ± 0.003*

* P < 0.05.

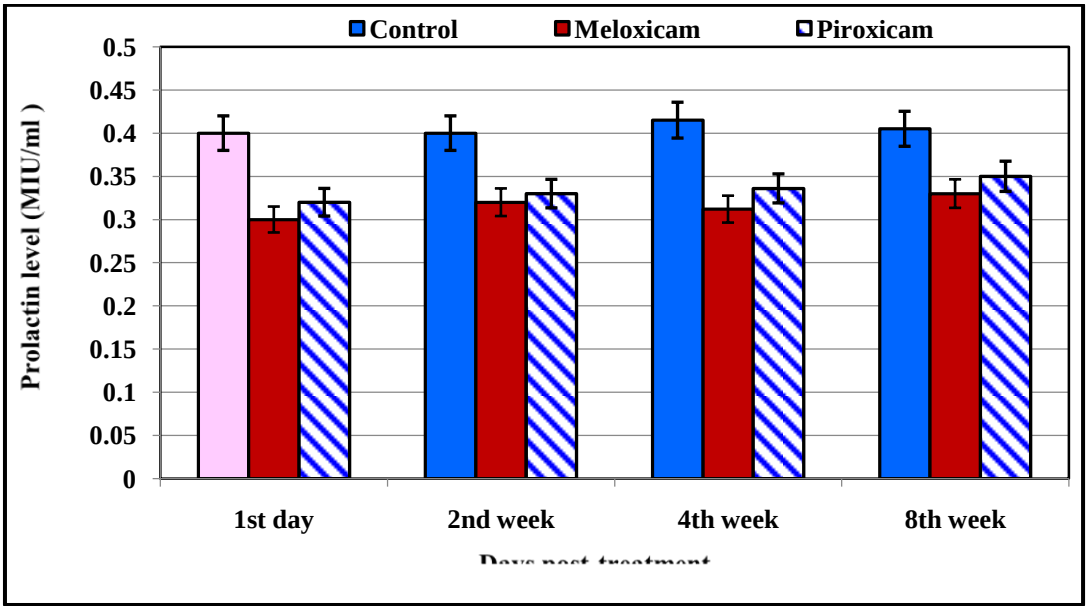


Fig 10: Effect of meloxicam, (0.13 mg/100 gmb.wt.) piroxicam (0.18 mg/100gm b.wt.) given I.M for successive 7 days on serum prolactin level of male rats.

2.7 Histopathological changes:

2.7.1 Effect of Meloxicam:

a) Testicles:

The male rat testicle of the group treated with meloxicam for successive 7 days showed normal histologic structure with normal germ cells proliferation at one day post treatment (Fig. 11). But after 2 weeks post drug administration the testicles revealed congestion of the testicular blood vessels (Fig. 12).

At 4 weeks post meloxicam administration in its recommeded dose for 7 days, the testicle demonstrated congestion of blood vessels with mild hypoplasia of germ cells of some germ nests (Fig. 13). Whereas, after 8 weeks post end of meloxicam treatment. The testicle showed focal hypoplasia of germ cells of some germ nests (Fig. 14).

In addition some germ nests showed necrosis and others with focal destruction of parenchyma (Fig. 15). Desquamation of germinal epithelium of the germ nest (seminiferous tubules) and germinal stages with increased thickness of intertubular tissue were also evident in testicles after 8 weeks post-treatment with meloxicam (Fig. 16).

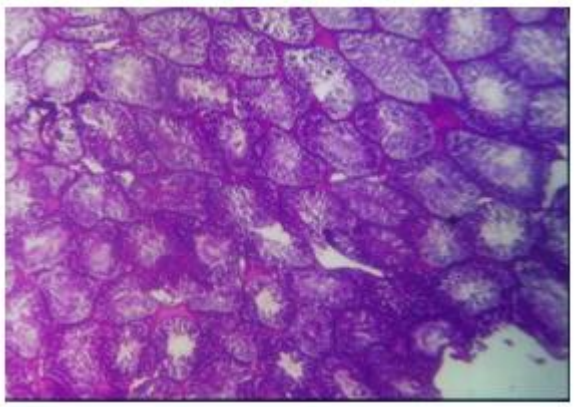


Fig 11: Photomicrograph of male rat testis one day post end of meloxicam administration showing normal histologic structure with normal germ cells proliferation (H & E x 400).

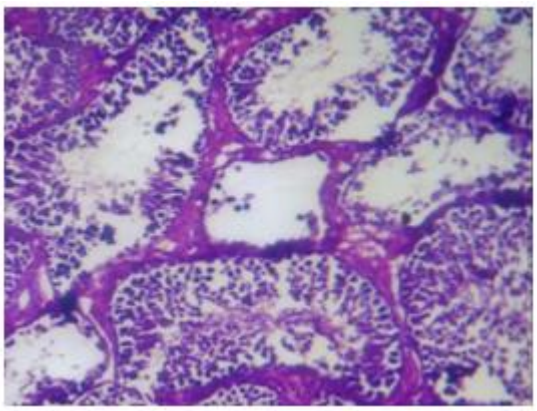


Fig 12: A photomicrograph of rat testis at 2 weeks post meloxicam administration showing congestion of testicular blood vessels (H & E x 400).

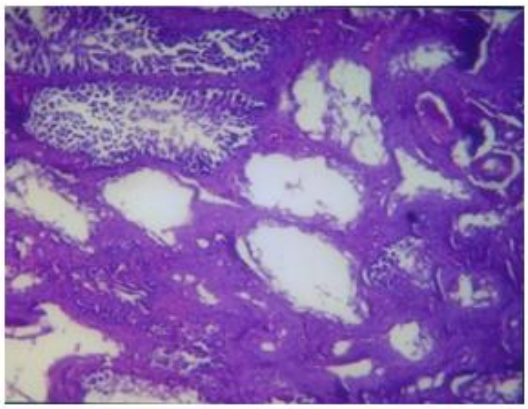


Fig 13: A photomicrograph of rat testis post 4 weeks of meloxicam administration on showing congestion of blood vessels with mild hypoplasia of germ cells of some germ nest (H & E x 400).

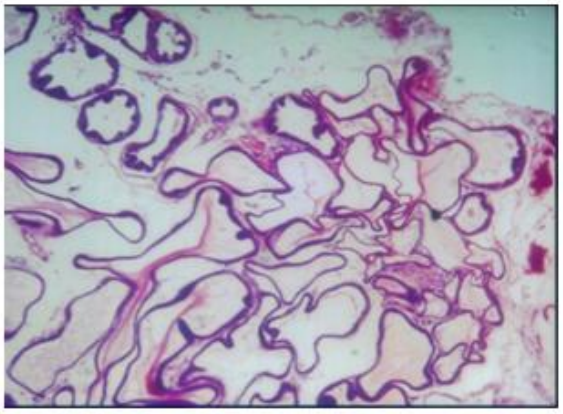


Fig. (14): A photomicrograph of rat testis 8 weeks post meloxicam administration showing focal hypoplasia of germ cells of some germ nests (H & E x 400).

b) Prostate gland:

The prostate gland of the group treated with meloxicam showed normal histological structure with intralumenal secretion (Fig. 17). While after two weeks post drug administration the prostate gland showed congestion of blood vessels (Fig. 18). Whereas, after 8 weeks post meloxicam administration, the prostate gland revealed degeneration of glandular epithelium with destruction of interstitial matrix (Fig. 19). Focal appearance of neoplastic germ cells within the germ nests as an early stage of seminoma were also evident.

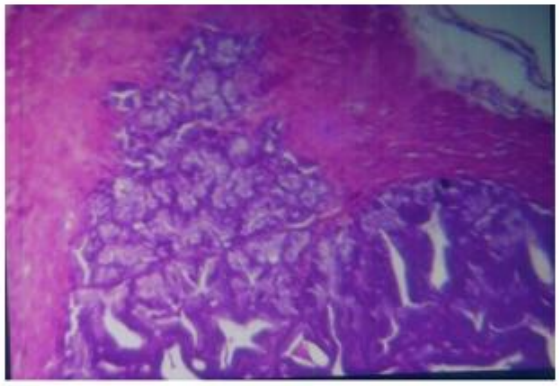


Fig. (15): A photomicrograph of rat testis 8 weeks post meloxicam administration showing some germ nests and necrosis of others with focal destruction of parenchyma (H & E x 400).

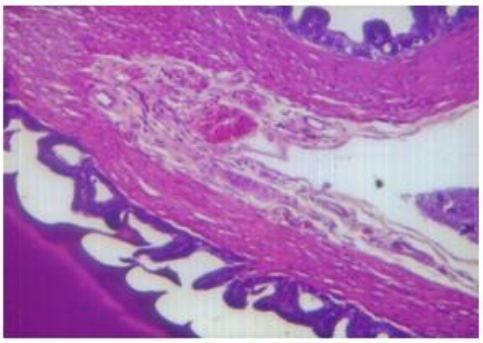


Fig. (16): A photomicrograph of rat testis 8 weeks post meloxicam administration showing desquamation of germinal epithelium of the germ nest (seminiferous tabules) and germinal stages with increased thickness of intertubular tissue (H & E x 400).

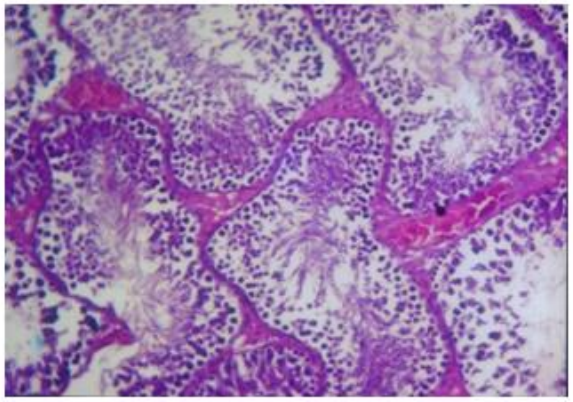


Fig 17: Photomicrograph male rat prostate one day post-meloxicam administration showing normal histologic structure with intraluminal secretion (H & E x 400).

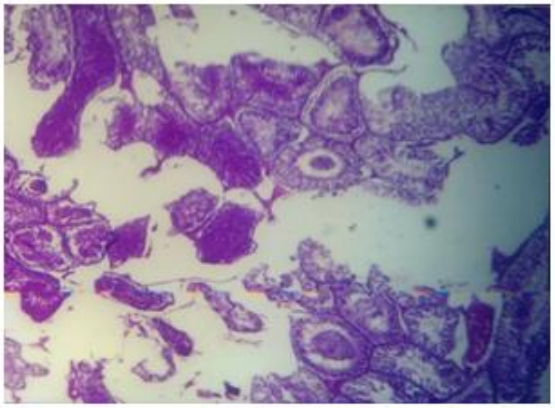


Fig 18: A photomicrograph of rat prostate at two weeks post meloxicam administration showing congestion of blood vessels (H & E x 400).

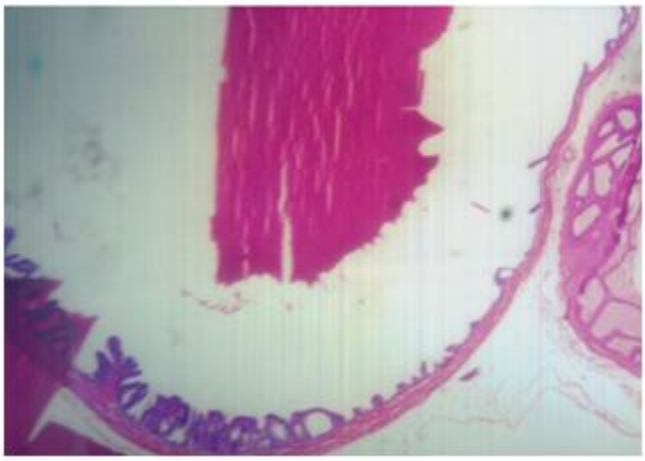


Fig 19: A photomicrograph of rat prostate gland, 8 weeks post meloxicam administration showing degeneration of glandular epithelium with destruction of interstitial matrix (H & E x 400).

c) Seminal vesicles:

The seminal vesicles of the rat group treated with meloxicam showed congestion of the blood bessels with perivascular fibroblast cells 4 weeks post drug administration (Fig. 20). While after 8 weeks post-drug administration, degenerative changes and desquamation of the mucosal epithelium was evident (Fig. 21 & 22). As well as congestion of the blood vessels (Fig. 23).

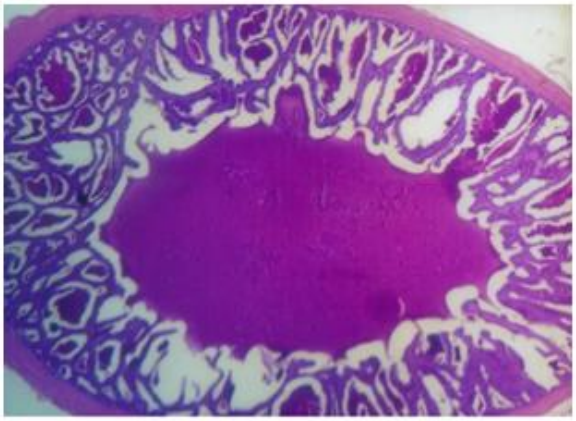


Fig 20: A photomicrograph of rat seminal vesicle 4 weeks post meloxicam administration showing congestion of the blood vessels with perivascular fibrosis (H & E x 400).

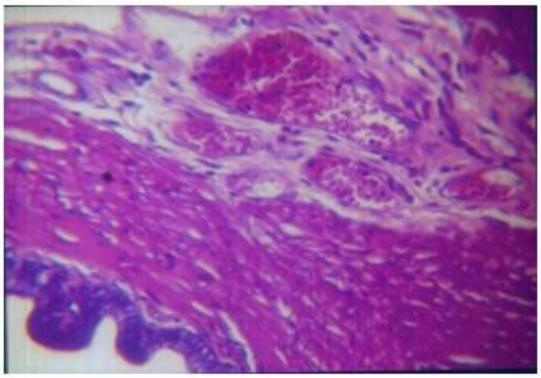


Fig 21: A photomicrograph of rat seminal vesicle 8 weeks post meloxicam administration showing degenerative changes of mucosal epithelium (H & E x 1000).

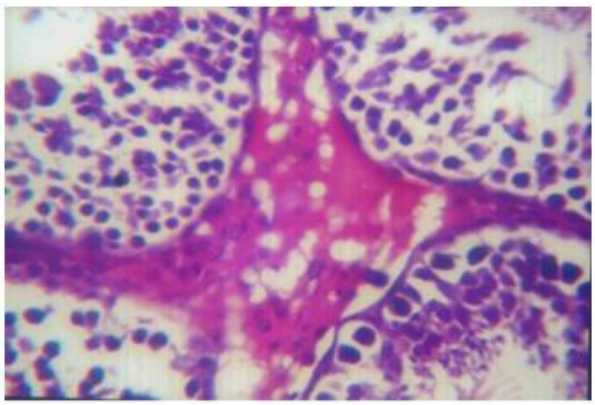


Fig 22: Aphotomicrograph of rat seminal vesicle 8 weeks post meloxicam administration showing desquamation of the mucosal epithelium (H & E x 400).

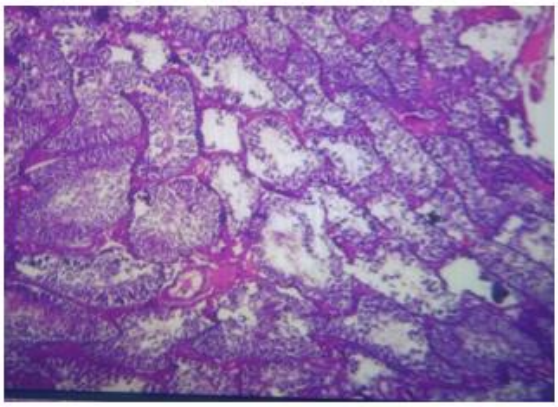


Fig 23: A photomicrograph of rat seminal vesicle 8 weeks post meloxicam administration showing congestion of the blood vessels (H & E x 400).

2.7.2Effect of piroxicam:

a) Testicles:

Two weeks post piroxicam administration, the testicles revealed excessive proliferation of germ cells and sperm production in the germ nest center (Fig. 24).

After 4 weeks post piroxicam administration there were vaculation of interstitial septa between seminiferous tubules (Fig. 25). While after 8 weeks post drug administration the testicle showed focal hypoplasia of germ cells of some germ nests. (Fig. 26). As well as congestion of the blood vessels with degeneration of most germ nests (Fig. 27).

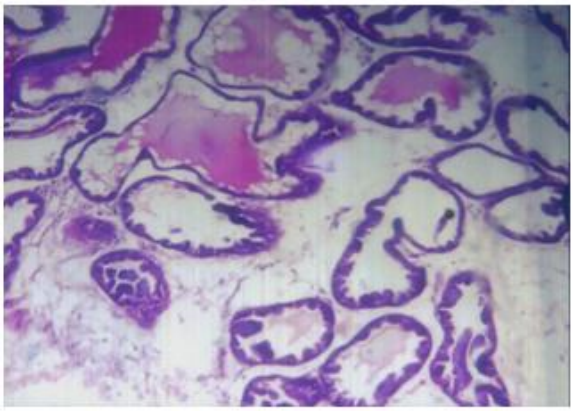


Fig 24: A photomicrograph of rat testis, two weeks post piroxicam administration showing excessive proliferation of germ cells and sperm production in the germ nest center (H & E x 400).

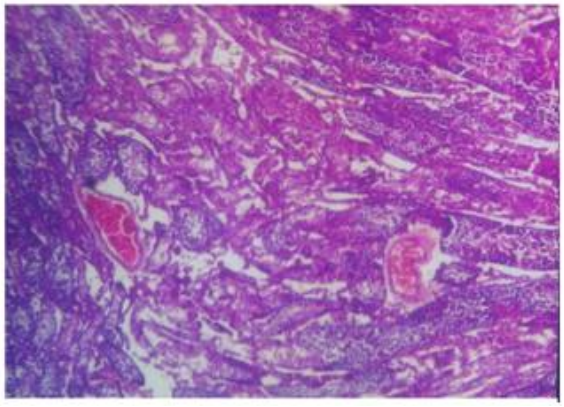


Fig25: A photomicrograph of rat testis 4 weeks post piroxicam administration showing vaculation of interstitial septo between seminiferous tubules (H & E x 1000).

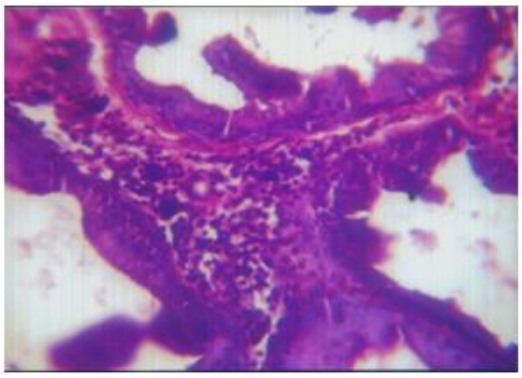


Fig 26: A photomicrograph of rat testis 8 weeks post piroxicam administration showing focal hypoplasia of germ cells of some germ nests (H & E x 400).

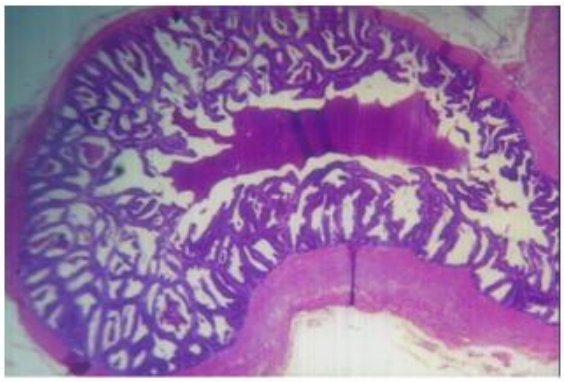


Fig 27: A photomicrograph of rat testis 8 weeks post piroxicam administration showing congestion of the blood vessels with degeneration of most germ nests (H & E x 400).

b) Prostate glands:

After 8 weeks post prioxicam administration, the prostate gland exhibited severe congestion of blood vessels (Fig. 28).

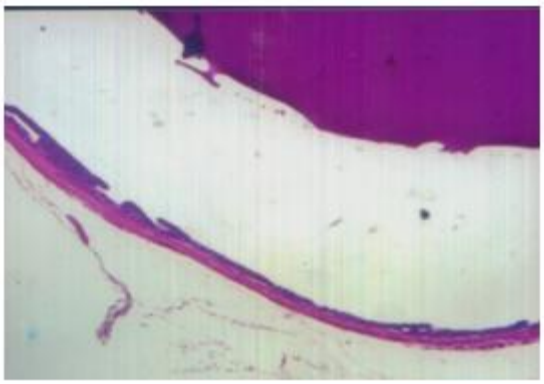


Fig 28: A photomicrograph of rat prostate 8 weeks post piroxiam administration showing severe congestion of blood vessels (H & E x 1000).

Seminal vesicle :
The seminal vesicle showed apparently normal structure and slightly narrow lumen two weeks post prioxicam administration (Fig. 29). While after 8 weeks post drug administration the seminal vesicle revealed disappearance of convoluted folds of interspersed mucosal columnar epithelium (Fig. 30).

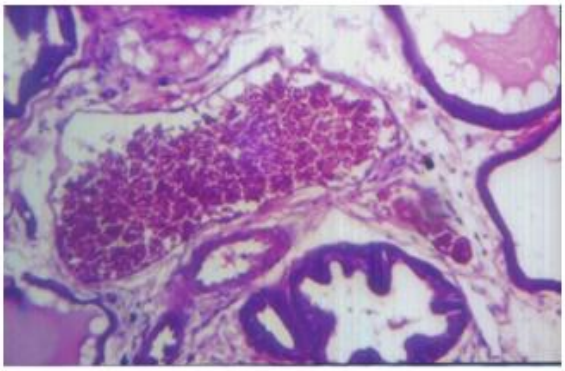


Fig 29: A photomicrograph of rat seminal vesicle two weeks post piroxicam administration showing apparently normal structure and slightly narrow lumen (H & E x 200).

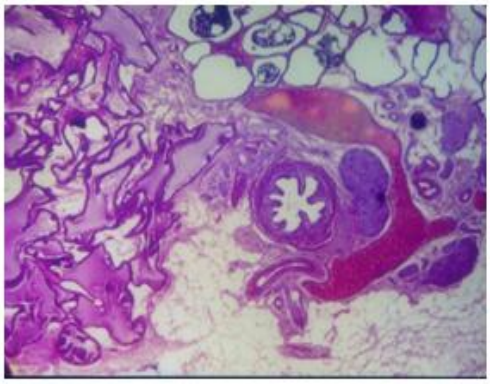


Fig 30: A photomicrograph of rat seminal vesicle 8 weeks post piroxicam administration showing disappearance of convoluted folds of interspersed mucosal columnar epithelium (H & E x 400).

III. Discussion

In the present study, the effect of meloxicam and /or piroxicam on male fertility was studied in rats. The duration of the study lasted for 8 weeks to cover complete spermatogenic cycle in rats which ranges from 48 – 56 days *(Clermont and Harvey, 1965).* The index weight of the sex organs (Testicles, seminal vesicle and prostate gland) was significantly decreased along the course of the study compared with control group. An effect which seems conceivable to be due to decreased level of testosterone hormone (free and total testosterone) evidenced in our study. This seems conceivable with the fact that testosterone is responsible for the growth and development of male secondary sex organs. Our results coincides with that obtained by *Ahmed (2011).* He injected meloxicam i.m. in a dose of (1.8 mg/kg) 3 times a week for successive 8 weeks and found that the index weight of the male sex organs was significantly decreased compared with control group. Moreover, our results were compatible with the histopathological findings observed in this work which revealed that meloxicam and piroxicam elicited histopathologcal changes represented by congestion of the testicular blood vessels and focal hypoplasia of germ cells of some germ nests. In addition some germ nests showed necrosis and others with focaldestruction of parenchym as well asdesquamation of germinal epithelium of the germ nests (Seminiferous tubules) were also evident after 8 weeks post-treatment with meloxicam.

Whereas, piroxicam afforded excessive proliferation of germ cells and sperm production in the germ nest center after 2 weeks and vacuolation of interstitial septa between seminiferous tubules after 4 weeks. While after 8 weeks, the testicles showed focal hypoplasia of germ cells of some germ nests as well as congestion of the blood vessels with degeneration of most germ nests.

The prostate gland of the group treated with meloxicam showed congestion of the blood vessels after 2 weeks and degeneration of the epithelium with destruction of interstitial matrix. Together with focal appearance of neoplastic germ cells within the germ nests as an early stage of seminoma were also evident.

Furthermore, piroxicam exhibited severe congestion of blood vessels as well as massive atrophy and destruction of prostatic gland epithelium with complete destruction of interstitial matrix and mononuclear cells infiltrating interstitial connective tissue.

The seminal vesicle of rat group treated with meloxicam showed congestion of the blood vessels with perivascular fibroblast cells 4 weeks post drug administration while after 8 weeks degenerative changes and desquamation of the mucosal epithelium and congestion of blood vessels were evident.

But with piroxicam the seminal vesicle showed disappearance of convoluted folds of interspersed mucosal columner epithelium after 8 weeks post drug administration.

The obtained results revealed that both meloxicam and piroxicam induced a significant decrease in serum gonadotrophins as well as serum testosterone. The decreased serum testosterone obtained in this study coincides with the fact that gonadotrophins are responsible for testosterone secretion *(Quintana et al., 2008).*

These results are in full agreement with *Shim et al., (2011)* who found that administration of meloxicam resulted in a significant decrease in testicular weight without significant changes in the weights of accessory glands.

This result is confirmed by the results obtained by *Alexander (1978) and Srikanth et al., (1999).* They reported that the development and maintenance of accessory organs and their secretions depends upon androgens.

The decreased level of testosterone hormone evidenced in this work by the decreased levels of serum gonadotrophins (LH & FSH) and degenerative changes of the testicles on one side. And on the other side the decreased level of testosterone observed in this study could be possibly attributed to the decreased synthesis of testosterone due to decreased level of testicular cholesterol reported by *Ahmed (2011)* as it is well documented that testosterone is synthesized from cholesterol.

Testosterone is a major circulating hormone which is essential for reproduction and maintenance of male sex characters. It is required for the attachment of different generations of germ cells in seminiferous tubules and therefore low level of intra-testicular testosterone may lead to detachment of germ cells from seminiferous epithelium and may initiate germ cell apoptosis and subsequent male infertility *(Lanco-Rodrigez and Martinez-Garcia, 1998).* This conclusion might be supported by the hypothesis that an agent acting directly on the brain, hypothalamus or anterior pituitary gland will indirectly affect the testes and well possibly affect sexual activity. Moreover, *Shim et al., (2011)* found alsothat meloxicam and tolfenamic penetrates the cerebrospinal fluid rapidly and thus induced its adverse effects on male fertility.

Regarding the effect on semen picture, the obtained results revealed that both drugs (Meloxicam and piroxicam) induced a significant decrease in sperm cell count, individual and mass motility at the end of the experiment (8 weeks) as well as a significant decrease in the percent of live/ dead and increased the percent of sperm abnormalities. The decreased sperm count indicates an adverse effects on spermatogenesis in rats administered the tested drugs impairing sperm motility in these rats indicating a defect in maintenance of motility.

These drugs might alter the epididymal secretory products or has a direct action on sperm motility and morphology *(Zaied, 2004 and Ballent et al., 2007).* The increased sperm abnormalities evidenced in this study by many primary abnormalities as double head, broken tailand long head in the meloxicam treated group. Whereas, in the piroxicam –treated group there were also many primary abnormalities such as Zegzag-shaped tail. These sperm abnormalities could be attributed to the inhibitory effect of both drugs on prostaglandin synthesis *(Dequeker et al., 1998)* as well as their molecular weight is less than 600 daltons. *Tso and Lasy (1975)* reported that several types of prostaglandins (PGE, PGF2) are claimed to disrupt the spermatogenesis and reduce sperm count in several species. The decreased sperm count induced by both drugs could be possibly attributed to the low concentration of testosterone evidenced in this study, as the sperm production in testes and its maturation in the epididymis is under, the control of testosterone *(Sharpe et al., 1992).*

It has been reported that many prostaglandin synthesis inhibitors like aspirin, indomethacin meloxicam, piroxicam reduce fertility in several animals species by impairing the spermatogenic process and decreasing gonadotrophins and testosterone concentration evidenced in this study *(Didolkar et al., 1985 and Quintana et al., 2008).*

Regarding the histopathological changes our results revealed that both drug afforded pathological changes in the testicles, seminal vesicle and prostate gland as previously discussed in the effect of the drugs on sex organs indexweight. Nearly similar results were obtained by *Ahmed (2011).* The degenerated changes observed in the testicles in response to administration of each drug alone for 7 days are supported by the finding of *Ahmed (2011),* he reported an increased level of testicular ALP and LDH leading to the degenerative changes that occur in the testicles, *(Turk et al., 1996 and Karjalainen et al., 2008).*

The activity of ALP in testicular tissue could be used as an indicator of testicular function and that the increase in testicular ALP reflect testicular damage (*Johnson, et al., 1970 and Karjalainea et al., 2008).*

Blackshaw&Elington(1970) and Clausen, (1969), mentioned that LDH is an enzyme that catalyzes the conversion of lactate to pyruvate. This is an important step in energy production in cells and plays an important metabolic role in sperm production. It may be necessary for maintaining the spermatozoa during their maturation in the epididymis and during their presence in the female reproductive tract by the utilization of lactate in these areas. It is located mainly in the interstitial tissue of both foetal and adult rat testes. In bull testis this enzyme has been found mainly in thespermatogonia and spermatocytes, with less activity in the interstitial tissue. As cell dye, its LDH is released and find its way into the blood, *(Clausen, 1969 and Blackshaw&Elington, 1970).*

The activities of LDH in testicular tissue are associated with the maturation of the germinal epithelial layer of seminiferous tubules *(Ante et al., 2004 and Srivastava et al., 1990).* The increased level of LDH in treated animal with the tested drugs suggests that these drugs induces deterioration of germinal epithelium *(Srivastava et al., 1990 and Srivastava and Vijayan, 1996).*

Aur et al., (1999) reported that tolfenamic acid and meloxicam treated male rats showed an increase in the level of testicular LDH and ALP and they attributed this effect to suppression of testosterone hormone.

These results were in accordance with *Agarwal and Said (2005),* they reported that, there is a different mechanisms for impairing male fertility by NSAID drugs such as aspirin and paracetamol or meloxicam and tolfenamic acid such as production of oxidative stress increasing cytochrome P_{450} activity, thereby boosting radical oxygen scavenger (ROS) generation and decrease male fertility.

Loscher and Blazaki, (1986), studied the effect of prolonged treatment with 4 NSAIDs (acetyl Salicylic acid, indomethacin, naproxen and phenylbutazone) on fertility in male rats. They found that all drugs except phenylbutazone decreased prostaglandin E-2 level in seminal fluid and reduced fertility significantly.

IV. Conclusion

The study concludes that giving meloxicam & piroxicam to male rats for 7 days has had negative effects on the level of reproductive hormones, weight of the genitals and sperm image, as well as the histopathological picture of the genitals, which makes us advised not to use these drugs in male animals.

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