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Safety evaluation of levofloxacin following repeated oral administration on liver in dual purpose chicken

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Abstract
The study was conducted in 30 to 40 day old healthy dual purpose chicken Indian Rock -3 (IR-3), a strain of White Plymouth Rock The safety evaluation of levofloxacin following the repeated oral administration was conducted in dual purpose chicken. The experimental birds were administered with levofloxacin at the dose rate of 10 mg/kg bw and 20mg/kg bw respectively directly for 28 days in dual purpose chicken. The estimation of serum biochemical parameters and histopathological findings of liver were conducted. There was a significant increase ($p< 0.05$) in AST, ALT and Alkaline Phosphatase' values in Groups III on day 21 and 28 in the experimental birds as compared to control group. Microscopically in Group II and Group III of experimental birds, section of liver showed mild dilatation of sinusoids with focal infiltration of mono nuclear inflammatory cells,vacuolar degeneration of hepatocytes, congestion of central vein, mild periportal proliferation and infiltration of mononuclear cells in the parenchyma. The birds were observed for clinical signs of toxicity, which were supported by increase in serum biochemical parameters and histopathological changes in the liver of dual purpose chicken. This is suggestive of administration of high dose of levofloxacin causes toxicity in dual purpose chicken.

Keywords: Dual purpose chicken, levofloxacin, liver, histopathology

1. Introduction
Levofloxacin, a third-generation fluoroquinolone, is the S-isomer of ofloxacin used to treat a number of bacterial infection like sinusitis, pneumonia, H. pylori infection, urinary tract infection, gastroeneteritis, Chronic prostatis, tuberculosis, meningitis and pelvic inflammatory diseases. It possesses excellent activity against gram-positive, gram-negative and anaerobic bacteria (North *et al.*, 1998) [19]. It also has more pronounced bactericidal activity particularly against organisms such as *Pseudomonas*, *Enterobacteriaceae* and *Klebsiella* spp (Klesel *et al.*, 1995) [12]. The bactericidal effect of levofloxacin is achieved through reversible binding to DNA gyrase and subsequent inhibition of bacterial DNA replication and transcription (Fu *et al.*, 1992) [9]. The levofloxacin distributes well to target body tissues, fluids and its uptake makes it suitable for use against intracellular pathogens. Levofloxacin's ability to bind to proteins in the body ranges from 24-38%. The levofloxacin acts by a concentration-dependent killing mechanism, whereby the optimal effect is attained by administration of high doses over a short period of time (Drusano *et al.*, 1993) [5] followed by a relatively prolonged postantibiotic effect (Aliabadi and Lees, 2001) [2]. The drug undergoes wide spread distribution into body tissues. The drug distributes well to the target body tissues and fluids in respiratory tract, skin, urine and prostate, and its uptake by cells makes it suitable for use against intracellular pathogens (Langtry and Lamb, 1998) [13].
Levofloxacin along with other fluoroquinolones such as gatifloxacin, moxifloxacin, grepafloxacin, trovafloxacin offer more favourable pharmacokinetic parameters such as higher AUC, C_{max} and longer elimination half-life than older compounds such as ciprofloxacin. Levofloxacin is metabolized in the liver to demethyl-levofloxacin and levofloxacin-N-oxide and excreted through the urine (Lubasch *et al.*, 2000) [15].
The good bioavailability, large volume of distribution, high C_{max}, AUC and pharmacokinetic-pharmacodynamic hybrid efficacy predictors, adverse effects indicate that administration of levofloxacin at 10 mg/kg bw by different routes may be highly efficacious against susceptible bacteria in turkeys (Aboubakr *et al.*,2014) [1]. The use of antibiotics in animal farming lead to risk of antibiotic residues in the final food product.

To protect the consumer from this risk, regulatory authorities have introduced several legislative initiatives such as the establishment of Maximum Residue Limits (MRLs) and development of other controls measures on food products. With the widespread and inadequate use of fluoroquinolones for animal growth and production, there is lack of recommended withdrawal period for fluroquinolones so accumulation of drug residues in the animal tissues (Martin *et al.*, 2007) [17].

Fluoroquinolones are frequently used in poultry production and human medicine with safety criteria, including withdrawal periods, doses and treatment duration, as their misuse and abuse may cause bacterial resistance and presence of residues in edible tissues. Consequently, the consumption of animal products with fluoroquinolone residues may result in transmission of resistant bacteria (Gouvea *et al.*, 2015) [10]. Elkholy *et al*. (2009) [6] reported the adverse effect of enrofloxacin preparations in laying hens following repeated oral administration at a dose rate 10 mg /kg bw once daily for five consecutive days. There was an increase in serum ALT, AST and ALP activities, serum glucose, cholesterol and creatinine levels in experimental birds compared to control laying hens.

Sadariya *et al*. (2010) [21] investigated the safety of moxifloxacin after repeated intramuscular administration at dose rate of 5 mg/kg bw at 24 h interval for 14 days in male and female wistar rats. The blood biochemical parameters (AST, ALT, ALP, Total bilirubin, total serum protein, serum albumin, globulin, serum creatinine, and urea were analyzed in the present study.The blood biochemical parameters were found to fluctuate within normal range and did not significantly ($p< 0.05$) differed in the treatment group corresponding to that control birds. Oda *et al*. (2014) [20] reported levofloxacin induced hepatotoxicity in rabbits after administered orally at the dose of 82 mg /kg bw once daily for four weeks. They reported that a significant increase in serum AST and ALT activities on first and fouthweek and a significant increase in serum activity of ALP only at the end of fourth week in the treatment group as compared to control group.

2. Materials and Method

The experimental birds (35 day old) were randomly allotted into three groups (n=30), Group I birds served as control (Distilled water), Group II and Group III birds were administered with levofloxacin at the dose rate of 10 mg/kg bw and 20 mg/kg bw respectively for five days directly into the crop using a thin plastic tube attached to a syringe for 28 days. The food was withheld for 12h before oral dosing but not water and water was provided *ad libitum* before the drug administration. The selection of the dosage based on, levofloxacin at 10 mg/kg bw considered as therapeutic dosage in the poultry birds (Varia *et al*., 2009; Banna *et al*., 2013) [23., 4], Therefore 20 mg/kg of levofloxacin was selected as high dose based on the therapeutic dosage of levofloxacin to see the any adverse effect with respect to serum biochemical analysis. The prior approval of the Institutional animal Ethics Committie (IAEC) was obtained before the commencement of the experiment(LPM/IAEC/181/2014, Date: 10/01/2014).

The serum samples used for the determination of biochemical parameters on day 0, 7, 14, 21 and 28 by using clinical biochemical analyzer - Microlab 300 (Vitalab Scientific, Netherlands). The serum biochemical parameters were estimated using commercially available diagnostic kits from ERBA Mannheim (Transasia Biomedicals Ltd, HP) by following the manufacturer instructions furnished in the leaflet supplied along with the diagnostic kit.

1. Aspartate aminotransferase (AST)
2. Alanine aminotransferase (ALT)
3. Alkaline Phosphatase (ALP)

2.1 Statistical analysis

The data were analyzed by using one-way ANOVA. The mean values and standard error of the different groups were compared by Duncan's multiple range test using Statistical Package for Social Sciences (SPSS16, 2010). Data were considered as significant from one another when $P\leq 0.05$.

2.2 Histopathological examination

After the collection of the blood for serum biochemical analysis, six birds from each group were randomly selected and sacrificed at weekly interval on day 0, 7, 14, 21 and 28 during the study period. The birds were subjected to a detailed post mortem examination and gross lesions if any were recorded. The samples of liver were collected, washed with normal saline and then collected in 10 percent neutral buffered formalin (NBF). They were processed through routine paraffin embedding technique. All the organs were processed for histopathology by cutting sections of 4µm thickness and stained with Haematoxylin and Eosin (Luna, 1968). The histolopathological lesions were observed in sections of various organs were systematically recorded and photomicrographs were taken using Zeiss AxioCam Erc5s microscope.

3. Results and Discussion

3.1 Serum biochemical parameters

The biochemical parameters (AST. ALT and ALP) were estimated from serum samples obtained on day 0,7,14,21 and 28 of experiment period after administration of levofloxacin in dual purpose chicken.

3.2 Serum aspartate aminotransferase (AST)

The mean AST values for levofloxacin in Group I (Control), Group II (10 mg/kg bw) and Group III (20 mg/kg bw) of experimental birds were measured at weekly interval and have been summarized in Table.1 and graphically represented in Fig. 1.

Table 1: Effect of levofloxacin on Aspartate aminotransferase activity (U/L) in dual purpose chicken

Days	Control	Levofloxacin 10 mg/kg bw (Mean ±SE)	Levofloxacin 20 mg/kg bw (Mean ±SE)
0	170.40±0.88	168.40±0.60[a]	172.32±0.65 [a]
7	210.34±0.20	214.24±0.90 [a]	218.64±0.80 [a]
14	216.44±0.13	224.30±0.78 [a]	230.64±0.64 [a]
21	218.97±0.64	219.58±0.90 [a]	250.65±0.90[b]
28	220.64±0.82	228.86±0.85 [a]	267.80±0.68 [b]

Values are mean ± SE n= 6, a: Non significant(p>0.05), b: Significant ($p< 0.05$)

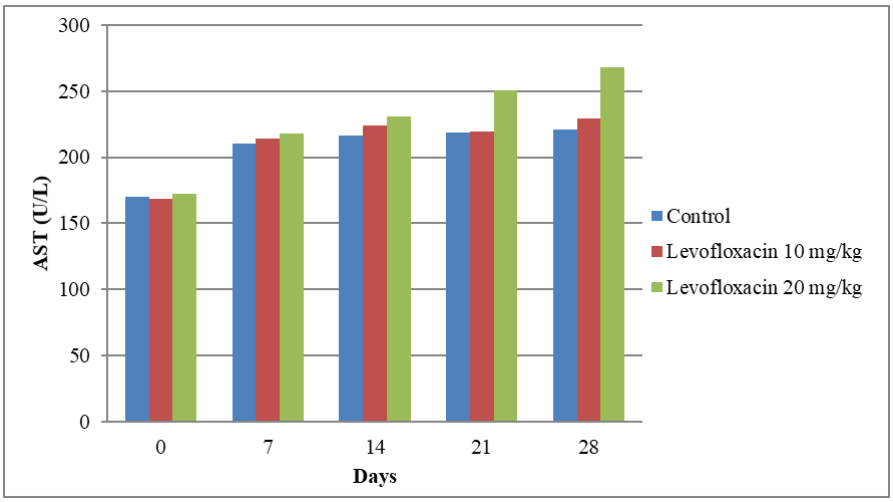

Fig 1: Effect of levofloxacin on Aspartate aminotransferase activity (U/L)in dual purpose chicken

There was a significant increase ($p< 0.05$) in AST values in Groups III on day 21 and 28 in the experimental birds as compared to control group.

There was no significant increase (P> 0.05) in AST values in Groups II on day 0,7,14, 21, 28 and in Groups III on day 0,7, 14 as compared to control group throughout the experiment. In the present study, a significant increase ($P< 0.05$) in AST activity in Groups III of the experimental birds on day 21 and 28 as compared to control group. This finding is supported with Oda *et al*. (2014) [20] who reported that a significant increase in serum AST value on first and four weeks after administration of levofloxacin hydrochloride at the dose of82 mg /kg bw through oral route once daily for four weeks in rabbits. Elkholy *et al*. (2009) [6] studied an increased in serum AST activities following repeated oral administration of enrofloxacin at 10 mg /kg bw once daily for five consecutive days in laying hens. Fatai *et al*. (2013) [8] reported an increase in AST activity after the administration of ciprofloxacin in rats for a period of five days.

3.3 Serum alanine aminotransferase (ALT)

The mean ALT values for levofloxacin in Group I (Control), Group II (10 mg/kg bw) and Group III (20 mg/kg bw) for experimental birds were measured at weekly interval and have been summarized in Table 2 and graphically represented in Fig.2.

There was a significant increase ($P< 0.05$) in ALT values in Groups III on day 21 and 28 in the experimental birds as compared to control group. There was no significant increase (P> 0.05) in ALT values in Groups II on day 0,7,14, 21, 28 and in Groups III on day 0, 7,14 as compared to control group throughout the experiment.

The present finding is in agreement with findings of Elkholy *et al.* (2009) [6] reported an increase in ALP activities following repeated oral administration enrofloxacin at 10 mg /kg bw once daily for five days in laying hens. Oda *et al*. (2014) [20] reported that a significant increase ($P< 0.05$) in serum ALT activity on first and four weeks after administration of levofloxacin hydrochloride at 82 mg /kg bw through oral route once daily for four weeks in rabbits. An increased in the ALT activity after the administration of ciprofloxacin in rats for period of five days was reported by Fatai *et al*., (2013) [8].

Table 2: Effect of levofloxacin on Alanine aminotransferase activity (U/L) in dual purposechicken

Days	Control	Levofloxacin 10 mg/kg bw (Mean ±SE)	Levofloxacin 20 mg/kg bw (Mean ±SE)
0	9.90±0.27	10.20±0.24[a]	10.70±0.78
7	12.92±0.52	12.48±0.42[a]	13.25±0.80[a]
14	12.10±0.47	12.64±0.18[a]	14.20±0.64[a]
21	12.26±0.28	13.02±0.90[a]	16.56±0.62[b]
28	12.48±0.73	13.42±0.40[a]	17.24±0.92[b]

Values are mean ± SE n= 6, a:Nonsignificant (p>0.05), b: Significant ($p< 0.05$)

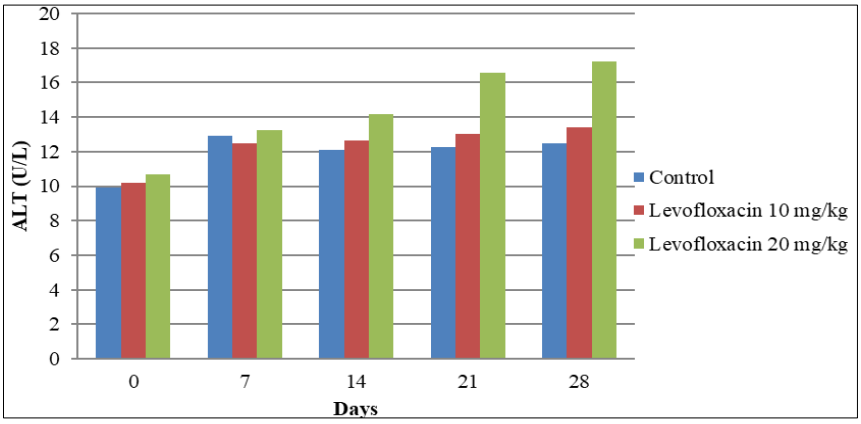

Fig 2: Effect of levofloxacin on Alanine aminotransferase (U/L) in dual purpose chicken

3.4 Alkaline Phosphatase (ALP)

The mean ALP values for levofloxacin in Group I (Control), Group II (10 mg/kg bw) and Group III (20 mg/kg bw) of experimental birds were measured at weekly interval and have been summarized in Table 3 and graphically represented in Fig.3.

In the present study, a significant increase ($P< 0.05$) in ALP activity in Group III of the experimental birds on day 21 and 28 as compared to control group. There was no significant increase (P>0.05) in ALP values in Groups II on day 0,7,14, 21, 28 and in Groups III on day 0, 7, 14 when compared to the control group throughout the experiment.

Table 3: Effect of levofloxacin on Alkaline phosphatase (U/L) in dual purpose chicken

Days	Control	Levofloxacin 10 mg/kg bw (Mean ±SE)	Levofloxacin 20 mg/kg bw (Mean ±SE)
0	2187±0.22	2201±0.24[a]	2206±0.06[a]
7	2194±0.80	2204±0.40[a]	2210±0.87[a]
14	2200±0.30	2216±0.98[a]	2221±0.97[a]
21	2202±0.96	2218±0.87[a]	2229±0.86[b]
28	2218±0.42	2230±0.60[a]	2243±0.79[b]

Values are mean ± SE n= 6, a:Nonsignificant(p>0.05), b: Significant ($p< 0.05$)

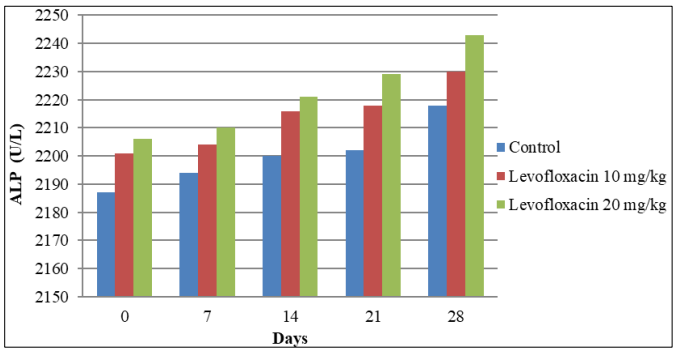

Fig 3: Effect of levofloxacin on Alkaline phosphatase (U/L) in dual purpose chicken

The above finding is in accordance with finding of Sureshkumar *et al.* (2013) [22] who reported an increase in alkaline phosphatase activity after administration of enrofloxacin at 10 mg/kg bw via drinking water for five days in birds. Elkholy *et al.* (2009) [6] reported an significant change in serum ALP activity after repeated oral administration of enrofloxacin at 10 mg/kg bw once daily for five days in laying hens. Fatai *et al.* (2013) [8] noticed that an increase in ALP values after the administration of ciprofloxacin in rats for a period of five days. Sadariya *et al.* (2010) [21] who reported that ALP values were found to fluctuate within normal range and did not differ significantly in the treatment group compared to control group after the administration of moxifloxacin at the dose of 5 mg/kg bw for 14 days in wistar rats.

The degeneration of hepatocytes and subsequent leakage of enzymes were the reasons attributed for increase in the levels for ALT, AST and ALP of serum enzymes (Leeson *et al.*, 1995) [14]. The degeneration of skeletal muscles and increase in the osteoblastic activity lead to an increase in the ALP activity (Falconer and King, 1970) [7].

3.5 Gross pathology

In the present study, gross pathological changes were observed in the liver of dual purpose chicken on weekly interval on day 0, 7,14,21 and 28 of the experimental study. The pathomorphological changes were observed in different groups and have been recorded as follows.

The Group I (control) birds showed no gross pathomorphological changes in all the organs examined during necropsy. The gross pathological lesions were observed on Group II and Group III on day 28 and day 21, 28 respectively in liver and kidney samples. In Group II, levofloxacin administered at 10 mg/kg bw, no gross pathological changes were observed on day 0,7,14 and 21. There was enlargement and congestion of liver on day 28 (Fig.2) compared to the control group (Fig 1). In Group III, levofloxcain administered at 20 mg/kg bw, there was no gross pathological change observed on day 0, 7 and 14. The liver samples were enlarged, congested, fatty liver (Fig.3) and enlarged, severely congested, fatty liver (Fig.4) on day 21 and day 28 respectively.

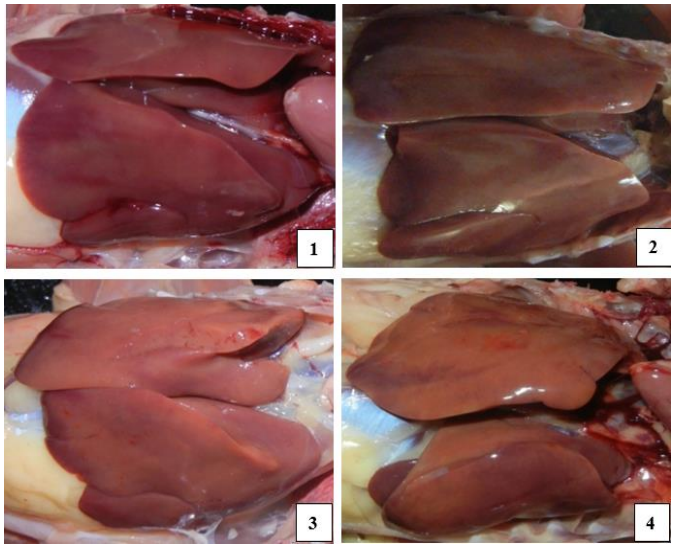

Fig 4: On day 21 and day 28 respectively.

3.6 Histopathology

The sections of liver in Groups II did not reveal any histopathological changes on day 0,7, 14 and day and in Group III on day 0 and 7 respectively throughout the experimental period compared to the control group (Fig.4).

The section of liver showed mild dilatation of sinusoids with focal infiltration of mono nuclear inflammatory cells, vacuolar degeneration of hepatocytes (Fig.5) and dilatation of sinusoids, congestion of central vein, infiltration of mono nuclear cells (Fig.6) in Group II on day 21 and 28 respectively.

The section of liver showed dilatation of sinusoids, vacuolar degeneration of hepatocytes and periportal infiltration of mono nuclear cells in group III on day 14 (Fig. 7). The congestion and oedema of central vein, mild periportal proliferation, infiltration of mono nuclear cells (Fig. 8) and nodular infiltration of mono nuclear inflammatory cells in the parechyma with periportal fibrosis, bile duct epithelial proliferation (Fig.9) on day 21and 28 respectively.

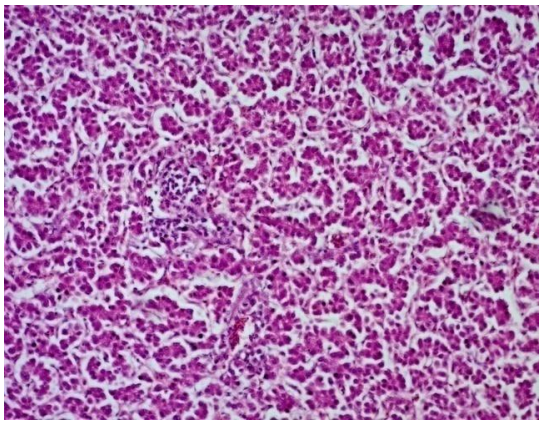

Fig 5: Normal architecture of hepatocytes.

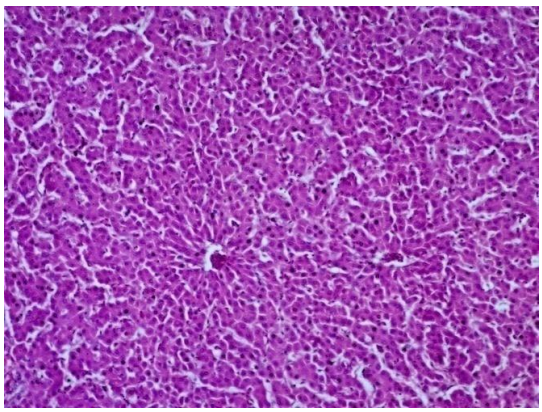

Fig 6: Mild dilatation of sinusoids with focal infiltration of mono nuclear inflammatory cells and vacuolar degeneration of hepatocytes.

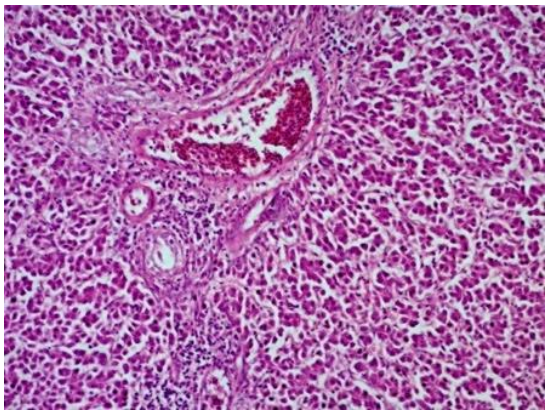

Fig 7: Dilatation of sinusoids, congestion of central vein and infiltration of mononuclear cells.

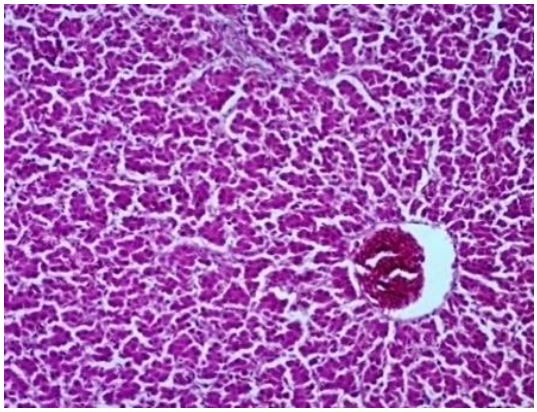

Fig 8: Dilatation of sinusoids, vacuolar degeneration of hepatocytes and periportal infiltration of mononuclear cells.

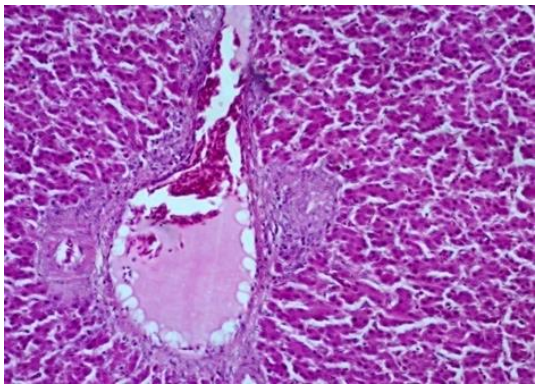

Fig 9: Dilatation of sinusoids, vacuolar degeneration of hepatocytes and periportal infiltration mononuclear cells

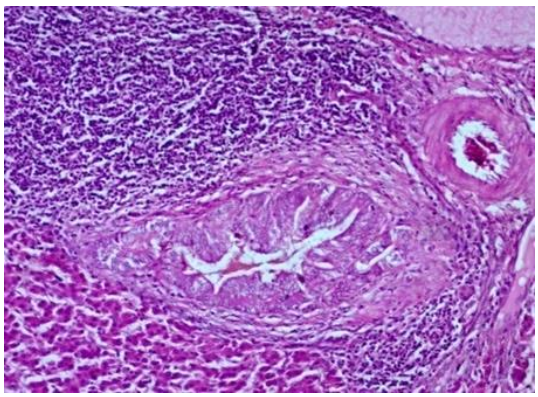

Fig.10: Dilatation of sinusoids, vacuolar degeneration of hepatocytes and periportal infiltration of mononuclear cells showing periportal mono nuclear cell infiltration and periportal fibrosis and bile duct epithelial proliferation.

These findings are in accordance with findings of Sureshkumar *et al*. (2013) [22] who reported that hepatocytes were swollen with vacuolated cytoplasm, degeneration, congestion and focal areas of infiltrated inflammatory cells after administration of enrofloxacin at the dose of 10 mg/kg bw via drinking water for five successive days. Nada and Shawi (2012) [18] reported degeneration and necrosis in the liver of juvenile rats treated with doses of ciprofloxacin (25 and 50 mg/ kg) compared to control rats. Amal and Daly (2011) [3] reported marked architectural disturbances of hepatic lobules, severe ballooning, degeneration, hepatic necrosis, rising of the leucocytic infiltrations with congested blood vessels and increased collagen fibers after the administration enrofloxacin in rats.

Histological observations such as degenerative and inflammatory changes, vacuolar degeneration of hepatocytes in liver and other organs of the present study uphold the alteration of the serum enzyme values in Group III experimental birds administered with 20 mg/kg bw of levofloxacin in dual purpose chicken.

4. Conclusion

In the present study, The experimental birds were administered with levofloxacin at the dose rate of 10 mg/kg bw and 20 mg/kg bw respectively directly for 28 days in dual purpose chicken. The birds were observed for clinical signs of toxicity, which were supported by increase in serum biochemical parameters (AST, ALT & ALP) with high dose of levofloxacin at 20 mg/kg bw for 28 days and histopathological changes in the liver of dual purpose chicken. This is suggestive of administration of high dose of levofloxacin causes toxicity in dual purpose chicken.

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