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Original Research Article

Clinicohaemato-Biochemical Alteration Due to Oral Feeding of Levofloxacin in Broiler Birds

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A B S T R A C T

Birds in the treatment group were administered with levofloxacin at the dose of 10mg/kg body weight, 20mg/kg body weight and 30mg/kg body weight via drinking water for 28 successive days, while the control group (untreated group) received non-Medicated water. Haematological parameters *viz.*, Haemoglobin (Hb), packed cell volume (PCV), Total erythrocyte count (TEC), Total leucocyte count (TLC) and Diffential leucocytes count (DLC) and Serum biochemical parameters viz., Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), total protein, albumin, blood urea nitrogen (BUN), uric acid and creatinine were estimated at 0, 3, 7, 14, 21 and 28 days intervals during the dosing and withdrawal periods, respectively. There was significant decrease (P0.05) in Hb, PCV, TEC, TLC and significant increase ($P<0.05$) in heterophiles and significant decrease ($P<0.05$) in lymphocytes. However there was significant increase ($P<0.05$) in AST, ALT, blood urea nitrogen (BUN), uric acid and creatinine levels and significant decrease ($P<0.05$) in total protein and albumin in the levofloxacin administered broiler chickens at all the time interval in comparison to control group.

Keywords

Broiler birds, Levofloxacin

Introduction

Fluoroquinolones are synthetic antimicrobial groups, which are widely used both in human and in veterinary medicine. These agents exert their antibacterial effect through the inhibition of DNA Gyrase, interfering with the super coiling of bacterial chromosomal material. They have a broad spectrum of activity against Gram-negative and Gram-Positive bacteria, Mycoplasma spp. and Rickettsia, which is included as resistant to beta-lactam antibiotics and sulphonamides. Chemotherapeutic use of fluoroquinolones (Ciprofloxacin, Norfloxacin, Pefloxacin), the 3rd generation of quinolone started only in the last decade as an effective antibacterial agent. Levofloxacin is the newer generation of quinolone now that is extensively used in poultry industry for treatment of bacterial diseases as it has improved pharmacokinetic and pharmacodynamics properties (Owens and Ambrose, 2005). The Safety and efficacy of Levofloxacin are well documented in lower respiratory tract

infections, skin & soft tissue infections and urinary tract infections, The safety profile seems advantageous over others Fluoroquinolones and the risk of phototoxicities, hepatotoxicity and neurotoxicity are very low (Norrby, 1991). However, indiscriminate use of levofloxacin in poultry industry has given rise to complications instead of benefits. The adverse effects arising from nonjudicious use of these fluoroquinolones are poorly understood in birds. The resistance of zoonotic bacteria, such as those belonging to the genera Salmonella and Campylobacter should be taken into account and prevented, as resistant bacteria or resistance genes may be transferred to humans through the consumption of poultry products.

The consumption of poultry products containing high fluoroquinolones residue levels is also a hazard for human health due to their adverse effects, including hypersensitivity reactions and intestinal micro flora imbalance, as well as to drug interactions, e.g., they may impair the therapeutic efficacy of other quinolone. Poultry pathologists are becoming more and more aware of the role of avian haematology as an aid in the diagnosis of many specific and non-specific diseases. The main objectives of present investigations are to study the effect of Levofloxacin on haematological and biochemical profile of broiler birds.

Materials and Methods

A study was conducted on oral feeding of levofloxacin in 120 broiler birds which divided into four groups i.e. T_0, T_1, T_2 and T_3. T_0 considered as control group. These birds were kept under observation for two weeks. Birds in the treatment group were administered with levofloxacin at the dose of 10mg/kg body weight, 20mg/kg body weight and 30mg/kg body weight via drinking water for 28 successive days, while the control group (untreated group) received non-Medicated water. Haematological parameters *viz.*, Hb, PCV, TEC, TLC and DLC with the help of Haematoanalyzer (Vet Scan) and Serum biochemical parameters viz., AST, ALT, total protein, albumin, blood urea nitrogen, uric acid and creatinine were estimated with diagnostic kit at 0, 3, 7, 14, 21 and 28 days intervals during the dosing and withdrawal periods, respectively at Department of Veterinary Pathology, Bihar Veterinary College, Patna.

Results and Discussion

The results of different haematological studies viz. haemoglobin concentration, packed cell volume, total erythrocyte counts and total differential leukocyte counts of hetrophiles and lymphocytes at various intervals of the experiment. There was significant ($P<0.05$) decrease in Hb concentration of group T_3 as compared to group T_2 and T_1 group throughout the observation period of 28 days while decrease in the Hb values of group T_2 & T_1 (in comparison to group T_3) was significant at 21st & 28th days only. This observation is similar to the findings of Haleema Al Nahari, (2014) who reported that haemoglobin concentration were significantly decreased in mice exposed to 0.5 and 1 mg/kg of Ciprofloxacin. Kumar *et al.*, (2009) revealed a significant decrease in Hb on 7 and 14 Day post treatment (DPT) in all treatment groups of birds indicating anaemia. Rashmi *et al.*, (2014) reported that Hb is significantly decreased level in treated (Group II, III and IV) female rat. Ellakany *et al.*, (2007) reported that treatment of 10-fold overdose resulted haemoglobin concentration showed decline in 29-34 days old broilers treated with enrofloxacin. A reference to this indicates that the mean

values of PCV in the group T_3 were comparatively lower than that in the group T_2 and T_1. The decline in the group T_3, in comparison to group T_2 and T_1 was significant ($P<0.05$) from day 3 to 28 of the observation period. Although a constant decrease in the values of PCV was also noticed in the group T_1 birds but these values (in comparison to controls) were not significant at any stage except at 28 days. Kumar *et al.,* (2009) revealed a significant decrease in PCV on 7 and 14 DPT in all treatment groups of birds. This observation is similar to the findings of Haleema Al Nahari, (2014) reported that total red blood cell (TEC) count and haemoglobin concentration were significantly decreased in mice exposed to 0.5 and 1 mg/kg of Ciprofloxacin for four weeks period. Kumar *et al.,* (2009) also reported that a significant decrease in TEC on 7 and 14 DPT in all treatment groups of birds. Rashmi *et al.,* (2014) reported that TEC significantly decreased level in treated (Group II, III and IV) female rat.

The reduction in RBC count may be due to macrocytic or normocytic anaemia. A significant ($P<0.05$) drop in TLC was observed in the group T_3 in comparison to group T_2 and T_1 from day 21 to 28 of experiment. Through the mean values of TLC in-group T_1 were slightly lower than that of the controls. However, difference was not significant at any stage of the experiment. Enumeration of total leukocyte count revealed a moderate decrease in TLC of both the levofloxacin fed groups T_2 and T_3. This observation is similar to the findings of Samah S. Oda *et al.,* (2014) reported that levofloxacin and gentamicin treated groups showed a significant increase in TLC at the end of the 1st and 4th weeks of the experiment in the rabbit. Rashmi *et al.,* (2014) reported that TLC significantly decreased in treated (Group II, III and IV) female rat. A slight significant ($P<0.05$) decreases in the relative percentage of lymphocytes with a corresponding significant ($P<0.05$) increase in the hetrophiles of the groups T_3, the difference was significant on day 21 and 28. Slight significant ($P<0.05$) decrease in the relative percentage of lymphocytes and significant ($P<0.05$) increase in hetrophiles was also observed in the group T_1 & T_2, but the difference was noticed in the relative percentage of Eosinophils, basophiles, and monocytes among different groups of experimental birds. Studies on the differential leukocyte counts of lymphocytes and hetrophiles revealed that leucopoenia was due to decrease in both lymphocytes and hetrophiles, the decline in hetrophiles count being more marked.

This observation is similar to the findings of Kumar *et al.,* (2009) reported that there was significant ($P<0.05$) decrease in lymphocytes with a corresponding significant ($P<0.05$) increase in the hetrophiles. Rashmi *et al.,* (2014) reported that TEC, Hb, and TLC showed significantly decreased level in treated (Group II, III and IV) female rat. Sharma *et al.,* (1994) demonstrated anaemia, eosiniphilia, leucocytopenia, thrombocytopenia, pancytopenia and raised prothrombin time in human after therapy with fluoroquinolones. Moderate increase in the activity of Alanine transaminasein the group T_3 that was significant ($P<0.05$) on days 21 and 28 in comparison to group T_2 birds. The increase in enzyme activity started from day 3 of the levofloxacin administration and continued up to the last day (28 days) of the observation. There was elevation in the values of aspartate transaminase (from day 14 to 28 of the experiment) but the Alanine transaminase levels remained in significantly ($P<0.05$) higher in the group T_2 and T_3 as compared to group T_1 birds.

Table.1 Effect of levofloxacin administration (10mg/kg body weight, in drinking water for 28 successive days) on Hb, PCV, TEC, TLC and DLC (data is shown as Mean±SE, n=30)

	Control	0	3	7	14	21	28
Hb	9.81±0.115	9.80±0.311	9.75±0.227	9.55^{a}±0.170	9.51^{a}±0.170	9.45^{ab}±0.206	9.24^{b}±0.095
PCV	31.75±0.478	31.69±0.853	31.63±0.750	31.50^{a}±0.629	31.32^{a}±0.478	31.25^{b}±0.478	31.19^{b}±0.108
TEC	4.75^{a}±0.095	4.85±0.251	4.83±0.150	4.74^{a}±0.125	4.70^{a}±0.082	4.68^{a}±0.169	4.69^{a}±0.123
TLC	30.710±0.235	30.820±0.588	30.770±0.622	30.650±0.537	30.600±0.233	30.550^{b}±0.114	30.272^{b}±0.270
Heterophil	28.05±1.77	28.15±1.70	28.34±1.71	28.46±1.79	28.71±1.81	28.84^{a} ±1.81	28.86^{a} ±1.74
Lymphocyte	61.05^{c}±1.33	61.16±1.22	60.91±0.96	60.18^{b}±1.41	59.93^{b}±1.16	59.46^{b}±1.06	59.28^{bc}±0.96
Eosinophils	2.77±0.23	2.83±0.29	2.85±0.25	2.88±0.18	2.91±0.15	2.93^{ab}±0.16	2.97^{a} ±0.18
Monocyte	6.50^{a} ±0.67	6.71±0.31	6.8±0.55	6.85±0.47	6.89^{a} ±0.64	6.92^{a} ±0.75	6.97^{a} ±0.84
Basophils	1.00±0.21	0.99±0.29	1.05±0.24	1.11±0.27	1.17±0.21	1.23±0.26	1.28±0.23

Values with similar superscript (column wise- a, b, c, d) differ significantly ($p<0.05$)

Table.2 Effect of levofloxacin administration (20mg/kg body weight, in drinking water for 28 successive days) on Hb, PCV, TEC, TLC and DLC (data is shown as Mean±SE, n=30)

	Control	0	3	7	14	21	28
Hb	9.85±0.150	9.65±0.239	9.25±0.129	9.12^{a}±0.129	9.05^{b}±0.216	9.85^{b}±0.170	8.65^{c}±0.170
PCV	31.80^{a}.±0.645	31.25±0.707	31.21±0.946	31.15^{b}±0.408	31.10^{b}±0.478	30.95^{b}±0.645	30.87^{b}±0.629
TEC	4.81^{a}±0.182	4.55±0.263	4.39±0.129	4.25^{b}±0.150	4.15^{b}±0.075	4.08^{b}±0.104	3.91^{b}±0.126
TLC	30.800±0.613	30.700±0.187	30.550±0.576	30.400±0.613	30.370±0.235	29.850^{bc}±0.159	29.675^{bc}±0.350
Heterophil	28.32±1.66	28.21±1.68	28.39 ±1.72	28.51±1.78	28.75±1.80	28.97^{a} ±1.78	29.15^{ab}±1.76
Lymphocyte	61.14±1.26	60.98±1.84	60.47±1.21	60.13^{b} ±1.35	59.79^{b}±1.09	59.35^{ab}±0.96	58.96^{b}±1.35
Eosinophils	2.74 ±0.19	2.86±0.21	2.89±0.27	2.91±0.23	2.96±0.25	3.05$^{a\,b}$ ±0.15	3.17$^{a\,b}$ ±0.14
Monocyte	6.40±0.81	6.75±0.39	6.81±0.51	6.85±0.68	6.89^{a} ±0.71	6.95^{a} ±0.67	7.05^{ab}±0.73
Basophils	1.04±0.36	0.97±0.28	1.03±0.20	1.09±0.23	1.11±0.25	1.21±0.23	1.27±0.25

Values with similar superscript (column wise- a, b, c, d) differ significantly ($p<0.05$)

Table.3 Effect of levofloxacin administration (30mg/kg body weight, in drinking water for 28 successive days) on Hb, PCV, TEC, TLC and DLC (data is shown as Mean±SE, n=30)

	Control	0	3	7	14	21	28
Hb	9.86±0.125	9.35±0.155	9.20±0.095	8.67^{b}±0.125	8.20^{bc}±0.182	7.90^{c}±0.129	7.20^{d}±0.141
PCV	31.87±0.957	31.15±0.631	31.02±0.408	30.82^{b}±0.629	30.65^{b}±0.707	30.54^{b}±0.610	30.11^{c}±0.645
TEC	4.88±0.141	4.44±0.336	4.23±0.129	4.05^{b}±0.085	3.81^{b}±0.081	3.75^{b}±0.170	3.72^{b}±0.129
TLC	30.850±0.576	30.600±0.144	30.370±0.594	30.100±0.537	30.000±0.224	29.237^{c}±0.178	29.001^{c}±0.206
Heterophil	28.42±1.71	28.29±1.65	28.79±1.80	28.84±1.83	29.16±1.75	29.39±1.77	29.91±1.78
Lymphocyte	61.17±1.36	60.78±1.76	59.85±1.39	59.23±1.45	58.63±0.99	58.15±1.13	57.15±1.19
Eosinophils	2.71±0.11	2.89±0.28	2.91±0.24	2.93±0.27	2.99±0.29	3.18^{b} ±0.17	3.26^{b} ±0.13
Monocyte	6.30 ±0.79	6.83±0.41	7.13±0.45	7.32±0.55	7.46±0.66	7.53±0.73	7.82±0.86
Basophils	1.06±0.25	0.95±0.25	1.02±0.27	1.08±0.18	1.14±0.29	1.20±0.27	1.26±0.19

Values with similar superscript (column wise- a, b, c, d) differ significantly ($p<0.05$)

Table.4 Effect of levofloxacin administration (10mg/kg body weight, in drinking water for 28 successive days) on ALT, AST, BUN, Creatinine, total albumin, total protein and Uric acid levels (data is shown as Mean±SE, n=30)

	Control	0	3	7	14	21	28
ALT	18.52±0.290	18.55±0.580	18.57±0.476	18.65 ±0.172	18.71±0.204	18.75±0.275	18.85±0.329
AST	156.01±2.39	156.12±2.04	156.15±2.28	156.32±2.28	156.47±2.83	156.53±3.51	156.72±3.68
BUN	4.67±0.052	4.81±0.102	4.86±0.202	4.87±0.221	4.90±0.070	4.94±0.087	4.96±0.084
Creatinine	0.24±0.20	0.24±0.18	0.25±0.09	0.27±0.01	0.27±0.02	0.30±0.07	0.31±0.08
Total Albumin	3.82±0.113	3.85±0.129	3.84±0.091	3.82±0.091	3.80±0.095	3.75±0.119	3.72±0.084
Total protein	5.71±0.053	5.74±0.129	5.72±0.091	5.70±0.091	5.68±0.095	5.65±0.119	5.62±0.084
Uric acid	4.71±0.231	4.71±0.094	4.73±0.111	4.75±0.112	4.76±0.085	4.79±0.070	4.85±0.098

Table.5 Effect of levofloxacin administration (20mg/kg body weight, in drinking water for 28 successive days) on ALT, AST, BUN, Creatinine, total albumin, total protein and Uric acid levels (data is shown as Mean±SE, n=30)

	Control	0	3	7	14	21	28
ALT	18.42±0.193	18.70±0.976	18.72±0.363	18.85±0.170	18.97±0.154	19.05±0.212	19.15±0.379
AST	156.08±2.05	156.17±3.14	156.25±1.25	159.18±2.29	162.28±1.37	163.45±2.69	164.28±4.26
BUN	4.42±0.120	4.82±0.205	4.88±0.131	4.92±0.185	5.02±0.088	5.55±0.064	6.55±0.132
Creatinine	0.26±0.12	0.26±0.04	0.26±0.12	0.29±0.05	0.35±0.09	0.43±0.11	0.58±0.46
Total Albumin	3.85±0.062	3.83±0.098	3.82±0.070	3.79±0.085	3.68±0.112	3.61±0.111	3.27±0.094
Total protein	5.75±0.062	5.67±0.098	5.67±0.070	5.62±0.085	5.55±0.112	5.52±0.111	5.45±0.094
Uric acid	4.66±0.213	4.73±0.198	4.77±0.175	4.80±0.052	4.95±0.032	5.15±0.071	5.26±0.095

Table.6 Effect of levofloxacin administration (30mg/kg body weight, in drinking water for 28 successive days) on ALT, AST, BUN, Creatinine, total albumin, total protein and Uric acid levels (data is shown as Mean±SE, n=30)

	Control	0	3	7	14	21	28
ALT	18.32±0.252	18.95±0.197	19.05±0.370	19.75±0.232	20.77±0.193	20.90±0.204	21.70±0.453
AST	156.15±2.10	156.26±2.04	160.19±2.28	160.86±2.28	171.65±2.83	194.21±3.51	196.23±3.68
BUN	4.25±0.062	4.85±0.240	4.93±0.129	4.99±0.648	5.20±0.108	5.76±0.082	7.05±0.096
Creatinine	0.28 ±0.22	0.28±0.05	0.36±0.10	0.44±0.09	0.57±0.07	0.66±0.10	0.79±0.01
Total Albumin	3.87±0.125	3.80±0.097	3.77±0.110	3.65±0.096	3.63±0.177	3.47±0.095	3.08±0.108
Total protein	5.76±0.125	5.65±0.097	5.63±0.110	5.51±0.096	4.49±0.177	4.43±0.095	4.10±0.108
Uric acid	4.66±0.213	4.76±0.198	4.81±0.077	4.87±0.062	5.08±0.048	5.32±0.097	5.92±0.043

Such results may be attributed to this increase could be regarded as a factor to increase the permeability and subsequent leakage of cellular enzyme due to the levofloxacin toxicity. Sugawara *et al.*, (1996) also reported an elevated serum enzymatic activity in broiler birds and monkey respectively after therapy with ciprofloxacin both in therapeutic dose and higher doses of the drug. A significant ($P<0.05$) drop in TSP of both the levofloxacin fed groups (T_2 and T_3) as compared to control T_0 & T_1 on 21 days onwards. The values started from day 14 and continued till last day of the experiments. The total serum protein values were lowest in the group T_2 and these differed significantly from that in the group T_3 on 21 days onwards. Such results may be attributed to liver damage and nephrotoxic effect induced by levofloxacin. Estimation of total serum proteins at various intervals revealed severe hypoproteinaemia in both the groups T_2 and T_3 as compared to control group. Niyogi, (1999) reported hypoproteinaemia in birds treated overdoses of ciprofloxacin, Samah *et al.*, (2014) also reported hypoproteinaemia and hypoalbuminaemia evident in levofloxacin treated group at 4^{th} week post-treatment. Haleema Al Nahari (2014) also reported that there is decrease in serum total protein of treated mice when compared with control group. A significant ($P<0.05$) drop in total albumin of both the levofloxacin fed groups (T_2 and T_3) as compared to control T_0 & T_1 on 21 days onwards. The values started from day 14 and continued till last day of the experiments. The total albumin values were lowest in the group T_3 and these differed significantly from that in the group T2 on 21 days onwards. Estimation of total serum albumin at various intervals revealed severe hypoalbunaemia in both the groups T_2 and T_3 as compared to T_1 and control group. Kumar *et al.*, (2009) revealed a significant decrease in A: G ratio in broiler birds. There was considerable elevation in the values of BUN in the group T_3 as compared to group T_2 and T_1, but this difference was not

significant (P<0.05) except on days 21 and 28. The values of BUN in the group T_1 were comparable to those of the controls. Estimation of blood urea nitrogen and creatinine in the blood of chickens showed significant increase in the levels of both these metabolites in the chickens; increase being significant on day 14 and 21 only. Elevation in the levels of these metabolites is suggestive of some degree of renal damage in the levofloxacin fed groups. Rashmi *et al.,* (2014) reported that aspartate aminotransferase, Alanine aminotransferase, BUN, creatinine showed significant increased level in treated groups. There was increase in serum creatinine level in the group T_3 birds but this increase in comparison by group T_2 and $T_1$was not significant except at days 21 and 28. The mean creatinine level in the group T_3 birds was more than that in the group T_1 and T_2. The difference was significant (P<0.05) after 28 day of levofloxacin feeding. Increase in serum creatinine concentration in high dose levofloxacin fed birds might be due to nephrotoxic action of levofloxacin, which causes renal impairment by destruction of epithelial cells of proximal and distal convoluted tubules and tubular damage. Samah *et al.,* (2014) reported serum urea and creatinine levels were significantly increased in levofloxacin treated group at both 1st and 4th weeks post-treatment. There was increase in serum uric acid level in the group T_3 birds but this increase in comparison by group T_2 and T_1 was not significant except at days 21 and 28. The mean creatinine level in the group T_3 birds was more than that in the group T_2 and the difference was significant (P<0.05) after 21 day of levofloxacin feeding. Haleema Al Nahari, (2014) reported that there is significant rises in serum uric acid and creatinine in treated mice compared with control. Kumar *et al.,* (2013) also reported that a significant but transient elevation in serum uric acid and creatinine was noticed. Moustafa *et al.,* (1998) reported that in broiler chicken administration of levofloxacin in high doses (100, 200 and 400 mg/kg body weight through drinking water) for long periods (6 weeks) was accompanied with adverse effects on different organs along with elevated levels of AST, ALT, ALP, urea, uric acid and creatinine, hypoproteinaemia and hypoalbuminaemia.

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