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Full Length Article

Toxico-pathological Effects of Parenteral Administration of Gentamicin in Growing Broilers

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Abstract

The present study was designed to investigate the toxicopathological effects induced by intramuscular administration of gentamicin in growing broilers. A total of 180 broiler chicks at four weeks of age were divided into 16 groups and each group was administered a single intramuscular injection of gentamicin varying from 0 to 120 mg/kg body weight. Mortality was 100% in the groups receiving gentamicin 70 mg/kg and above. Feed intake and body weight of gentamicin administered groups was lower than control. The birds administered 0, 10 and 20 mg/kg gentamicin did not exhibit any clinical signs, while those in higher dose groups exhibited depression, sitting on hocks, lack of interest in feed, increased water intake, watery diarrhea and emaciation. Hemorrhagic and swollen kidneys bulging out from bony socket and mild swollen liver with discolored areas were consistent gross findings. Microscopically, kidneys showed severe congestion and tubular necrosis. Total serum protein and albumen was significantly lower in groups receiving higher doses of gentamicin as compared with control. Serum ALT and creatinine values were higher in gentamicin groups as compared with 0 and 10 mg/kg groups indicating nephrotoxic and hepatotoxic effects. It is concluded that gentamicin at higher doses resulted in poor growth and severe nephrotoxic and hepatotoxic effects.

Keywords: Gentamicin; Toxicity; Chicken; Pathology; Serum chemistry; Kidney; Liver

Introduction

Poultry industry produces animal proteins for human consumption most effectively and economically within the shortest possible time (Hosseinzadeh *et al*., 2010). The basic role of poultry production is turning feed stuffs into meat (Hafez, 2011). Poultry industry in Pakistan is a cheapest source of quality protein for masses.

Gentamicin, an aminoglycoside antibiotic is widely used for the treatment of various infectious diseases in veterinary and human medicine. Due to its poor absorption from digestive tract, it is administered intramuscularly. Its parental administration leads to high concentrations in renal cortex and internal ear. The frequent clinical findings of gentamicin toxicity included nephrotoxicity and ototoxicity (Huy *et al.,* 1983).

Gentamicin is extensively used as a treatment of different poultry diseases including fowl cholera, salmonellosis etc. The vertically transmitted diseases like mycoplasma had been controlled by dipping the hatching eggs in gentamicin solution (Booth *et al.,* 1988). Early chick mortality due to bacterial infections is also prevented by administration of gentamicin in day-old chicks. In day old chicks no observable effect level of gentamicin was 10 mg/kg body weight, however, at higher dose level different pathological changes including enlarged and swollen kidneys, swollen liver, decreased serum total protein, albumen and higher concentrations of serum ALT, creatinine and urea were observed in dose related manners (Saleemi *et al*., 2009). Occasionally gentamicin is also co-administered with killed vaccines for the treatment and prevention of bacterial infections. Experimental and clinical gentamicin toxicity in commercial White Leghorn birds has been reported to produce high mortality and toxicopathological changes in kidneys and liver (Khan *et al*., 2008; Islam *et al*., 2011). However, no published data is available about gentamicin toxicity in growing broilers except partial presentation of this study in FAVA-OIE congress Thailand by Javed *et al*. (2008). Current study was presented in the profligate use of gentamicin in avian species in Pakistan convinced to inquire the morphological alterations induced by its toxicity in growing broiler birds. The results of the present study would be helpful to identify the clinical signs and pathological lesions associated with gentamicin toxicity in broiler birds in field conditions.

Materials and Methods

Birds and Management

A total of 180 broiler chicks of 4 weeks of age procured

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from a commercial poultry farm were reared under standard housing and managemental conditions. Birds were offered commercial broiler feed having 21% protein (Damiri *et al*., 2012) and water *ad libitum*.

In the first experiment 120 broiler birds were divided into 12 groups (A-L) having 10 birds in each and administered gentamicin (Gentafar®, 10% Farvet, Holland) in pectoral muscles at a dose rate varying from 0-120 mg/kg body weight, respectively. In second experiment 60 birds were divided in 6 groups (A1, B1, D1, E1, F1 and H1) having 10 birds in each and administered gentamicin (Gentafar®, 10% Farvet, Holland) in pectoral muscles at a dose rate of 0, 10, 30, 40. 50 and 70 mg/kg body weight, respectively. Both experiments continued for four weeks.

Parameters Studied

Parameter studied in exp.1 included feed intake (daily), clinical signs (twice daily), body weight (weekly) and mortality. While in exp. 2 five birds were sacrificed on week 1 and remaining at the end of experiment. The blood was collected for serum chemistry. The serum biochemical parameters including total proteins and albumin were determined by Biuret and dye binding techniques (Varley *et al*., 1980). Serum creatinine and ALT were determined by commercially available kits. The necropsy examination of killed and dead birds during the experiment was performed for gross lesions on different visceral organs. Relative organ weights were calculated as % of body weight. Different visceral organs were fixed in 10% neutral bufferd formalin and processed for routine histopathological examination (Hassan *et al*., 2012).

Statistical Analysis

The experimental data obtained were subjected to analysis of variance test and different group means were compared by Duncan's multiple range tests using M-Stat-C. The level of significance was $p \leq 0.05$.

Results

Experiment 1

Feed consumption and body weight: Feed intake of birds administered various doses of gentamicin has been presented in Table 1. In weeks 1 and 2 feed intake of group A was significantly higher from all other groups and group H had the lowest feed intake. In week 3-5 feed intake of all the groups was significantly lower from group A except group B, which was non-significantly different.

The body weight of different groups administered gentamicin has been presented in Table 2. In first week body weight of the birds in group A (control) was significantly higher than all other groups and lowest body weight was observed in group G, which was significantly different from all other groups. This trend continued in week 3 to 5 and birds in all experimental groups had significantly lower body weights compared with control group (A). The decrease in body weight occurred in a dose related manner.

Clinical Signs

The birds of group A, B and C did not exhibit any clinical signs, their behavior remained normal throughout experimental period. Interest in the feed and drinking water of these groups was normal. These birds showed normal response to the attendants entering into shed. In group D, E and F, depression was observed in 5, 4 and 5 birds, respectively, soon after administration of gentamicin. It persisted for 8-12 h and then birds became normal. Almost 100% birds in the groups G, H, I and J showed severe depression by sitting on hock joints soon after gentamicin injection. Water intake was increased throughout the length of experiment. Watery diarrhea was a consistent feature. The birds progressively became emaciated and had prominent keel bone. Gross and microscopic lesions of both experiments are described in experiment 2.

Mortality

Mortality of birds in experiment 1 has been presented in Table 2. In the groups administered 70 mg/kg gentamicin and higher doses showed 100% mortality. There was no mortality in the groups administered 0-40 mg/kg gentamicin. In group F and G (50 and 60 mg/kg gentamicin) mortality was 33.33%.

Experiment 2

Relative Organ Weights (% of body weight): Relative organ weights in different groups are presented in Table 3.

Liver: In week 1 the relative weight of liver in all the groups was significantly higher from control group A1 and was highest in group H1. In week 4 liver weights of all the groups were significantly higher from control except group B1 which was nonsignificantly different.

Heart: In weeks 1 and 4, the relative weight of heart was significantly higher in groups D1, E1, F1 and G1 in comparison with group A1. Group B1 remained nonsignificantly different from control.

Kidneys: In week 1, all the experimental groups (B1-H1) had significantly higher relative weight of kidneys compared with the control. On week 4 groups B1, D1 were non-significantly different from control group, while all the remaining groups had significantly higher relative weights of kidneys than that of control.

Spleen: In week1 the relative weight of spleen was nonsignificantly different from control in groups B1 and D1, whereas it was significantly higher in remaining groups. In week 4 groups F1 and G1 had significantly higher weights of spleen compared with control.

Table 1: Feed intake and body weight of broiler birds injected different doses of gentamicin (Mean ± SD) Experiment 1

Groups	Week 1	Week 2	Week 3	Week 4	Week 5
			Feed intake (g /bird/day)		
A (0 mg/kg)	125.9±4.9a	141.9±4.8a	153.0±3.4a	164.7±3.4a	179.1±3.4a
B (10 mg/kg)	117.0±3.8b	132.3±5.4b	149.4±6.1a	164.4±2.8a	176.0±4.3a
C (20 mg/kg)	118.0±3.7b	126.7±2.6c	140.9±4.0b	157.3±5.2b	170.1±2.6b
D (30 mg/kg)	115.3±3.6b	124.3±2.6c	132.9±3.7c	145.0±3.4c	160.7±3.6c
E (40/mg/kg)	106.0±4.3c	119.7±3.0d	130.0±3.8c	137.9±2.2d	146.1±2.8d
F (50 mg/kg)	96.0±4.3d	106.1±3.0e	114.3±3.0d	124.1±3.5e	135.0±3.6e
G (60 mg/kg)	86.0±4.3e	99.3±3.9f	112.3±3.5d	122.6±3.9e	132.4±2.8e
			Body weights (g)		
A (0 mg/kg)	1360±114 a	1660±80 a	1800±73 a	2050±79 a	2190±96a
B (10 mg/kg)	1200±158 b	1430±49 b	1235±70 b	1865±96 b	2045±80b
C (20 mg/kg)	1120±130 b	1355±96 bc	1465±80 c	1655±87 c	1815±43c
D (30 mg/kg)	1100±79b c	1265±84 c	1395±65 cd	1475±121 d	1605±134d
E (40/mg/kg)	990±74 cd	1110±80 d	1300±73 d	1335±91 e	1495±102d
F (50 mg/kg)	900±47 de	1005±76 de	1050±107 e	1100±79 f	1250±116e
G (60 mg/kg)	820±65 e	960±72 e	1000±73 e	1050±68 f	1135±.52e

Values in each column within a parameter followed by different small letters are statistically different $p \leq 0.05$

Table 2: Mortality in broiler birds administered with various levels of gentamicin in experiment 1

Groups	Week 1	Week 2	Week 3	Week 4	Total mortality (#)	Total mortality (%)
A (0 mg/kg)	0	0	0	0	0	0
B (10 mg/kg)	0	0	0	0	0	0
C (20 mg/kg)	0	0	0	0	0	0
D (30 mg/kg)	0	0	0	0	0	0
E (40/mg/kg)	0	0	0	0	0	0
F (50 mg/kg)	0	3	0	0	3	33.33
G (60 mg/kg)	0	3	0	0	3	33.33
H (70 mg/kg)	3	7	0	0	10	100
I (80 mg/kg)	10	0	0	0	10	100
J (90 mg/kg)	10	0	0	0	10	100
K (100/mg/kg)	10	0	0	0	10	100
L (120 mg/kg)	10	0	0	0	10	100

Table 3: Relative organ weights of broilers birds injected different doses of gentamicin (Mean±SD) in Experiment 2

Groups	Liver	Heart	Kidney	Spleen
		Week 1		
A1 (0 mg/kg)	1.8±. 05 d	0.4±0.05 c	0.7±0.04 e	0.07±0.0 b
B1 (10 mg/kg)	2.5±0.3 c	0.5±0.03 bc	0.9±0.2 d	0.09±0.04 b
D1 (30 mg/kg)	2.5±0.06 c	0.7±0.2 b	0.9±0.1 d	0.06±0.03 b
E1 (40 mg/kg)	2.5±0.3 ab	0.6±0.1 b	1.2±0.1 c	0.16±0.04 a
F1 (50 mg/kg)	3.7±0.07 b	0.7±0.1 b	1.4±0.1 b	0.16±0.02 a
H1 (70 mg/kg)	7.3±0.8 a	1.0±0.1 a	1.9±0.2 a	0.16±0.07 a
		Week 4		
A1 (0 mg/kg)	1.8±0.03 c	0.4±0.05 d	0.67±0.05 c	.07±0.00 c
B1 (10 mg/kg)	2.2±0.18 c	0.4±0.06 dc	0.69±0.06 c	.08±0.03 bc
D1 (30 mg/kg)	4.0±0.40 b	0.5±0.06 b	0.92±0.05 c	.10±0.03 bc
E1 (40 mg/kg)	4.2±0.83 b	0.8±0.04 a	1.17±0.16 b	.10±0.04 bc
F1 (50 mg/kg)	7.7±1.25 a	0.9±0.14 a	1.80±0.30 a	.14±0.02 a
H1 (70 mg/kg)	8.2±0.90 a	0.8±0.16 ab	1.84±0.32 a	.13±0.02 ab

Values in each column followed by different small letters are statistically different $p \leq 0.05$

Serum-biochemistry: The results of serum chemistry are presented in Table 4.

Serum total protein: In week 1 groups D1 and E1 had higher total protein levels compared with control. While all the remaining groups were non-significantly different from control group. Similar trend was observed in week 4.

Serum albumin: In week 1, groups D1 and E1 had significantly higher while F1 and H1 had significantly lower values from control. In week 4 only group E1 had albumen value higher than control, while groups F1 and H1 were significantly lower from control group A1.

Serum ALT: In week 1 and 4 groups D1, E1, F1and G1 had significantly higher ALT values compared with group A1.

Serum creatinine: In week 1 and 4 all the groups had significantly higher values as compared with control group.

Gross Lesions

Kidneys: The birds killed from groups A1, B1 and D1 at week 1 did not show any gross lesions. While groups E1, F1 and H1 showed severe nephritis. In week 4 birds from groups A1-E1 did not show any gross lesions, however, birds from group F1 and H1 showed severe nephritis and discolored areas on kidneys (Fig. 1). In some birds, kidneys showed urates deposit. Similar lesions were observed in dead birds in experiment 1.

Liver: Birds killed from groups A1-E1 did not show any lesion at week 1, while birds sacrificed from groups F1 and H1 indicated mild swelling. No such lesions were observed in these groups at week 4. Birds from groups F1 and G1 showed swollen, fragile livers. Similar gross lesions were observed in dead bird in experiment 1.

Histopathology

Kidneys: No microscopic lesions were present in kidneys of group A1. In group B1 at week1, kidneys showed mild degree of congestion. Kidneys of 2 out of 5 birds exhibited degenerative and necrotic changes in the proximal convoluted tubules. These changes were characterized by pyknotic nuclei. Bowman's spaces were clear but dilated in some birds. At week 4 kidneys of 2 out of 5 birds had areas of tubular necrosis characterized by pyknotic nuclei in epithelium of proximal convoluted tubules.

Table 4: Serum biochemical parameters of broilers birds administered different dose levels of gentamicin (Mean ± SD) in experiment 2

Groups	Total Proteins (g/100 mL)	Albumin (g/100 mL)	ALT (IU/µL)	Creatinine (mg/100 mL)
		Week 1		
A1 (0 mg/kg)	4.00±0.01 c	1.66±0.02 c	16.0±0.69 e	0.6±0.02 e
B1 (10 mg/kg)	4.08±0.06 c	1.72±0.03 bc	15.8±1.13 e	0.66±0.01 e
D1 (30 mg/kg)	4.29±0.12 b	1.81±0.02 ab	21.9±1.25 d	1.02±0.05 d
E1 (40 mg/kg)	4.68±0.10 a	1.83±0.04 a	29.2±0.99 c	1.23±0.07 c
F1 (50 mg/kg)	3.83±0.12 d	1.13±0.10 e	36.5±1.35 b	1.43±0.09 b
H1 (70 mg/kg)	3.40±0.11 e	1.24±0.14 d	47.1±1.52 a	1.73±0.07 a
		Week 4		
A1 (0 mg/kg)	4.01±0.01 c	1.70±0.02 b	16.0±1.19 e	0.61±0.02 f
B1 (10 mg/kg)	4.30±0.14 b	1.70±0.02 b	15.7±1.05 e	0.73±0.02 e
D1 (30 mg/kg)	4.40±0.12 b	1.83±0.03 b	24.0±1.04 d	1.20±0.07 d
E1 (40 mg/kg)	4.75±0.04 a	2.07±0.14 a	32.0±1.16 c	1.39±0.03 c
F1 (50 mg/kg)	3.42±0.35 e	1.27±0.21 c	41.0±1.29 b	1.63±0.12 b
H1 (70 mg/kg)	3.73±0.16 d	1.29±0.20 c	47.0±1.30 a	1.83±0.12 a

Values in each column followed by different small letters are statistically different $p \leq 0.05$

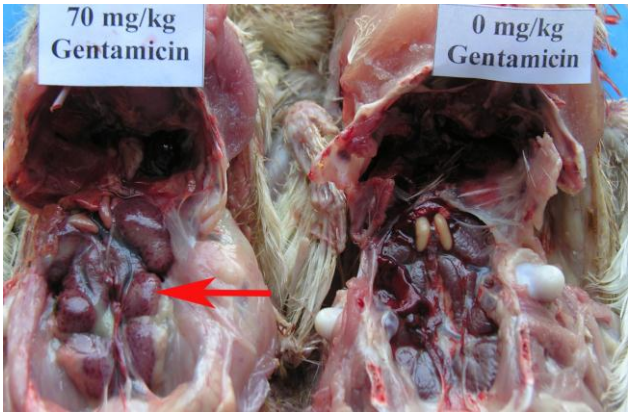

Fig. 1: Photograph of kidneys of broiler birds administered gentamicin (70 mg/kg bwt.) showing swollen kidneys (left) and normal kidneys in control group (right)

In group D1 at week 1 kidneys exhibited severe congestion and tubular necrosis. Necrosis was characterized by pyknosis, karyorhexis and karyolysis of nuclei in tubular epithelial cells. Granulation of cytoplasm of tubular epithelium was evident. Some birds showed wide spread areas of pyknotic nuclei in tubular epithelium of proximal convoluted tubules. Glomeruli were congested. Similar changes were observed in birds sacrificed on week 4. Similar lesions but more intense lesions were observed group E1.

In group F1 all the birds sacrificed on weeks 1 and 4 had kidneys exhibiting severe congestion and tubular necrosis. Blood vessels of the kidneys were congested. Necrosis of the epithelium of proximal convoluted tubules was characterized by pyknosis, karyorhexis and karyolysis. Vacuolation of cytoplasm of tubular epithelium was present. All the birds showed wide spread areas of tubular necrosis. In Group H1 Birds slaughtered on week 1 had kidneys with severe congestion and tubular necrosis. Vacuolation of cytoplasm of tubular epithelium was present. Proliferation of cells in glomeruli was observed in some birds. Extensive areas of tubular necrosis were present in the kidneys of all the groups (Fig. 2). No histopathology could be performed on week 4 because all the birds died in week 2 of the experiment.

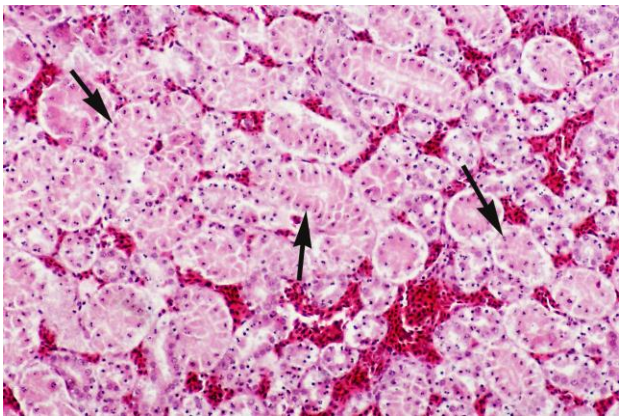

Fig. 2: Photomicrograph of kidneys of broiler birds in group H1 showing necrotic changes (pyknosis and karyohexsis) indicated by arrows (H and E staining 200X)

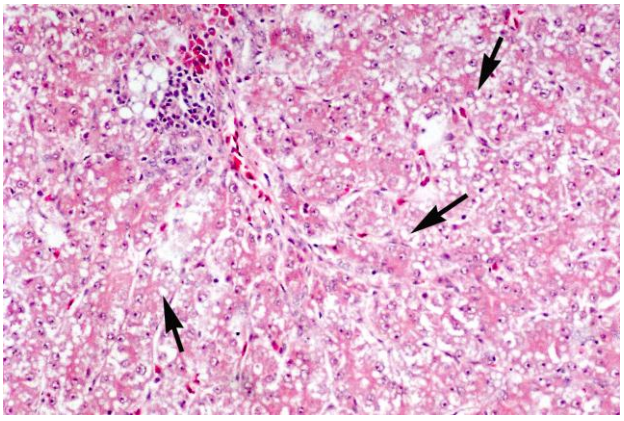

Fig. 3: Photomicrograph of liver of growing broiler birds of group F1 showing vacuolar degeneration (H and E staining 200X)

Liver: In Group A1 liver of the birds sacrificed at weeks 1 and 4 showed normal histological pattern. In groups B1 birds liver was similar to control group.

In groups D1, E1 and F1 at week 1, liver showed severe congestion and fatty change of hepatocytes. Blood vessels were hyperemic and sinusoid spaces dilated. Hepatocytic cytoplasm contained small to large multiple round clear vacuoles with sharp borders. In many hepatocytes nuclei were pushed to one side. Some birds exhibited cellular infiltration by monocytes and granulocytes. Birds of group H1 at week 1 had fatty change of hepatocytes with severe congestion of parenchyma. At many places hepatocyts were disintegrated leaving empty spaces (Fig. 3). Chromatin material was clumping and attached to nuclear membrane. Sinusoid spaces were dilated.

Discussion

Gentamicin, an aminoglycoside is extensively used in poultry and animals medicines for treatment of infectious diseases. Gentamicin is nephrotoxic and ototoxic (Begg and Barclay, 1995; Landau and Kher, 1997; Islam *et al.,* 2011). Its toxicity is attributed to its accumulation in renal tubular epithelial cells and endolymph of ear (Laureat *et al.,* 1983; Duff, 1992). Due to extensive use of gentamicin in poultry medicine, it was assumed that many cases of unexplained nephritis, hepatitis and high mortality might be due to nephrotoxic substances among which gentamicin is the important one. There was a dire need to establish a link between pathomorphological alterations and serumbiochemical changes induced by gentamicin in avian species.

In the current experiments birds administered gentamicin up to 60 mg/kg exhibited significant decrease in body weight gain, which might be due to anorexia and depression developed soon after gentamicin administration. There is no information on this aspect of decreased weight gain and feed intake induced by gentamicin in growing broilers. However, similar results have been presented in day old broiler chicks and White Leghorn pullets (Khan *et al*., 2008; Saleemi *et al*., 2009).

In the present experiments no clinical signs and behavioral alterations were observed up to 20 mg/kg gentamicin, suggesting this level as tolerable for the birds. In higher dose groups (30 and 40 mg/kg) a transient depression and anorexia followed by recovery was observed. It indicated moderate toxicity induced by gentamicin at these levels. These findings were in line with different studies in day old broiler chicks and commercial white leghorn layers (Khan *et al*., 2008: Saleemi *et al.*, 2009). Similar clinical signs have been observed in field cases in White Leghorn cockerels by Islam *et al*. (2011). Gentamicin administered at higher concentrations resulted in mortality varying from 30 to 100% at 70 mg/kg b wt. and above doses. Similar clinical signs and mortality was also observed in red tail hawks where 100% mortality was observed at 20 mg /kg administered twice daily (Bird *et al.,* 1983). One day-old broiler chicks and white layers also exhibited similar mortality (Khan *et al.*, 2008; Saleemi *et al*., 2009). In present study increased levels of creatinine and ALT were observed in birds administered 30 mg/kg and higher levels of gentamicin suggested a nephrotoxicity and hepatotoxicity of gentamicin. Many authors have reported an increase in serum creatinine and ALT following gentamicin administration in birds (Bird *et al.*, 1983; Itoh and Okada, 1993; Khan *et al.*, 2008; Saleemi *et al.*, 2009), laboratory animals (Kahn *et al.*, 1980; Walzl, 1982). However, a non-significant variation in serum creatinine and ALT in birds given 10 mg/kg suggested that this level might be nontoxic to broiler chicks. A decreased in total proteins and albumin contents of the birds administered gentamicin suggested a decrease in synthesis of serum proteins or excessive excretion/loss through damaged kidneys (Cowan *et al.*, 1980). As serum proteins synthesis occurs in liver, a severely demaged liver may also lead to decreased protien synthesis (Benjamin, 1978; Muhammad *et al.,* 2012). Liver of the birds administered 30 mg and above levels of gentamicin showed an injurious effect. Liver injury accompanied with anorexia in the birds might have resulted in decreased serum protein levels, increased in liver specific enzymes following gentamicin administration is also reported earlier (Itoh and Okada, 1993; Saleemi *et al*., 2009).

The gross lesions observed in kidney in the present study included swelling, congestion and hemorrhages. Histopathologically, tubular cell necrosis and presence of casts in the collecting tubules were the prominent features in birds given 30 mg/kg and above levels of gentamicin. Similar to our results tubular necrosis was a consistent finding in gentamicin toxicity reported by different researchers in different species including rats (McMartin *et al.,* 1982), horses (Godber *et al.,* 1985), avian species (Khan *et al*., 2008; Saleemi *et al*., 2009; Islam *et al*., 2011) and newborn puppies (Cowan *et al.,* 1980). How little information is available in growing meat type chicken (Javed *et al*., 2008). Mild degenerative changes in kidney of 10 mg/kg group were accompanied by non-significant elevation in serum creatinine suggesting that this level was non-toxic to the birds. Gentamicin after removal from the serum is accumulated in renal tubular cells and produced phospholipidosis (Laureat *et al.,* 1983; Beauchamp *et al.,* 1991). It could be assumed that gentamicin administered was retained in kidneys and caused a progressive damage.

Patho-morphological Changes in liver at 30 mg /kg comprised of fatty change which increased in severity and frequency with increase in dose levels. Many authors have reported injury to the liver based upon by elevated serum enzymes like ALT, AST, decreased serum protein and albumin (Kahn *et al.,* 1980; McMartin *et al*., 1982; Walzl, 1982; Bird *et al.,* 1983; Itoh and Okada, 1993; Khan *et al*., 2008; Saleemi *et al*., 2009). Toxic metabolites released by

damaged and impaired functioning of kidney could also result in hepatic injury. Emaciation observed in different group was accompanied by swollen kidney, liver and hemorrhages on the different organs including heart. This association of the lesions and clinical signs suggested that kidney and liver injuries followed by gentamicin administration could be the major reasons for anorexia and subsequent emaciation of the birds.

In conclusion, anorexia, increased water consumption, watery diarrhea and mortality were consistent findings. Macroscopically birds showed nephritis, hepatomegaly and hemorrhages on different organs including heart and skeletal muscles. Prominent histopathological changes in kidney and liver were tubular necrosis and fatty change, respectively. There was decrease in levels of serum protein and albumin and increase in ALT and creatinine. It can be concluded that parenteral administration of 10 mg gentamicin/kg b.wt was safe to the bird, whereas 60 mg/kg and above levels were highly toxic to the birds.

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