



Effects of gentamicin on growth performance and hemato-biochemical parameters in mice

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ABSTRACT

The study was outlaid & performed in order to investigate the effects of gentamicin on hemato-biochemical study and growth performance changes of mice. In this research 32 mice were randomly divided into 4 equal groups (n=8) namely A, B, C, and D. Group D was kept as control and fed with normal broiler pellet along with 0.06 ml of normal saline administered through intramuscular route for consecutive 10 days. Mice of group A, B and C were maintained as treated groups and given 0.12ml, 0.06ml and 0.03ml of gentamicin sulfate respectively by I/M route also for a 10 day period. Pediatric dose of gentamicin (7.5mg/kg B.Wt) was followed as a standard. Group A was considered as high dose, group B as normal dose and lastly, group C as half dose to be compared with the pediatric dose. The effects of gentamicin in the development of physiological and pathological alterations in mice were evaluated based on weight gain, biochemical parameters and hematology. The findings showed that, the mean initial body weight of all groups of approximately 60 days old (day 0 of experiment) were almost similar (A,B,C and D; 36.93±2.38g, 35.81±2.03g, 36.06±2.83g and 36.06±3.78g respectively). The differences between values were insignificant. Although, it showed much variation when recorded at the 5th day of the experiment. Group A and D showed significant (P<0.05) decrease in body weight (34.13±1.85g, 31.71±3.10g respectively) whereas, Group B and C showed increase in body weight (38.21±1.99g, 36.40±1.89g respectively) as compared to the day 0 body weight. In addition, On day 10 all the groups (A, B, C and D) showed increase (P<0.05) in body weight (38.95±1.83g, 38.63±1.50g, 37.61±1.73g and 33.96±1.09g respectively). In case of hematological parameters, erythrocyte number (TEC), hemoglobin concentration (Hb) and packed cell volume (PCV) increased significantly in group B (7.95±1.16 millions/cc, 8.05±.28gm/dl, 31±1.35% respectively) as compared with control. Total leukocyte count (TLC) showed a different scenario as the value was recorded highest in group A (7.99±0.11 thousand/cc) compared with control. In case of differential leukocyte count (DLC) the percentage of different cells showed great variation amongst the groups as compared with the control. Percentage of neutrophil and monocyte recorded highest in Group B (34.25±1.25%, 2.25±.48% respectively), eosinophil in group A (3±1.25%), lymphocyte in group C (64.67±1.33%). In the biochemical study, the level of cholesterol was recorded highest (P<0.05) in group B (122.74±9.37gm/dl). Similarly, the other parameters (serum creatinine, triglyceride and high density lipoprotein) were significantly higher in group B (0.45±.06 mg/dl, P<0.05; 211.96±49.13mg/dl, P<0.01 and 71.85±1.98mg/dl, p<0.01 respectively) than that of all groups as compared with the control. One of the aims of the research was to elucidate the fact that, whether or not the pediatric dose of gentamicin is safe for administration. On the basis of the findings and observations of the present study, it can be concluded that, administration of pediatric dose of gentamicin might be able to cause some changes in growth performance, hematological and biochemical blood profile but the changes of values would not exceed the reference ranges of these parameters. So, gentamicin if administered at pediatric dose is safe.

INTRODUCTION

Aminoglycoside antibiotics, especially gentamicin, constitute a very important weapon for veterinarians against gram-negative and few gram-positive bacterial infections. Like other antibiotics gentamicin is not free from toxic effects

both in human being and livestock. Gentamicin can induce ototoxicity and nephrotoxicity (Ali et al., 1992) because both organs (ear and kidney) have higher than normal concentration of phospholipids in their cellular matrices. Cationic aminoglycosides are chemically attracted to

anionic membrane phospholipids. Among the aminoglycosides, gentamicin preferentially accumulates in renal cortex resulting nephrotoxicity. Like other aminoglycosides gentamicin also initiate toxicosis by perturbation of renal proximal tubular cell membrane structure (Ali et al., 1992; Beauchamp et al., 1992). The cationic gentamicin is chemically attracted to the anionic phospholipids in the cell membranes of the proximal tubular cells. The renal proximal tubules actively take up gentamicin; concentration in the renal cortex is far greater than those observed concurrently in the serum and other tissues. Studies also have demonstrated a substantially higher renal cortical concentration of gentamicin compared with other tissues in humans (Schentag et al., 1977), rats (Luft et al., 1978), dogs (Cowan et al., 1980), cats (Jernigan et al., 1988), sheep (Brown et al., 1985), lambs (Weisman et al., 1982), cattle (Haddad et al., 1987), pigs (Riond and Reviere 1988) and birds (Bush et al., 1981). Substantial concentrations are also found in the renal medulla, liver, spleen and lungs in sheep, cattle, birds and rats. Occasionally renal medullary concentration is substantially higher than the concentration found in liver, spleen and lungs (Schentag and Jusko, 1977). Therefore the toxicity of gentamicin must take into account as problem relating to their hazardous effects upon human beings, animals and birds. For this reason an attempt has been made to study the adverse effects of gentamicin, if any, on some clinical, hematological and serological parameters in mice, a species of significant importance among laboratory animals.

Gentamicin is commonly used aminoglycoside antibiotic but nephrotoxicity are the most common adverse reactions (Rybak and Ramkumar, 2007). Aminoglycoside nephrotoxicity is characterized by decreased urine concentration capacity, tubular proteinuria, mild glycosuria, decreased ammonium excretion and lowering of glomerular filtration rate (Kaloyanides and Pastoriza-Munoz, 1980). *In vitro* studies have demonstrated that aminoglycoside enhances phospholipid membrane peroxidation (Walker and Shah, 1987 and Ramasamy et al., 1986) reported that there is an increase in renal cortical lipid peroxidation in gentamicin treated mice.

Drug-induced nephrotoxicity is an important cause of renal failure. Aminoglycosides throughout the endocytic pathway are taken up into the epithelial cells of the renal proximal tubules and stay there for a long time, which leads to nephrotoxicity. Acidic phospholipids, broadly distributed in the plasma membranes in various tissues, were considered to be the binding site of aminoglycosides in brush-border membrane of proximal tubular cells (Nagai and Takano, 2004). Hydroxyl radicals play a role in the pathogenesis of gentamicin nephrotoxicity, gentamicin can induce suppression of $\text{Na}^{(+)}\text{-K}^{(+)}\text{-ATP}$ ase activity and DNA synthesis in rats proximal tubules leading to renal injury; this injury may be relevant to reactive oxygen metabolites generated by gentamicin. Renal cortical mitochondrion is the source of reactive oxygen metabolites, which induces renal injury (Nephrol Dial Transplant. 1994; 9 Suppl 4:135-40). Very few studies of histopathology were reported in literature regarding histopathology of gentamicin induced renal failure in mice. So, the present study is taken up to record the biochemical investigation and hematological change in body of mice.

Aminoglycosides and aminocyclitols are antibiotics frequently used in veterinary and human medicine against gram-negative and some gram-positive microorganisms. It has been reported that they may cause permanent or transient changes in the blood parameters related to kidney function. There are publications in sheep (Lashev et al., 2001), rats (Young et al., 1978), humans (Schentag et al., 1987), and cats (Russel et al., 1988) with results supporting this hypothesis, whereas some reports confirm the opposite opinion in rabbits (Brion et al., 1984), mice (Yazar et al., 2003), cows (Huang et al., 2005), and dogs (Nagai et al., 2004). However, it is possible that aminoglycosides induce changes in some biochemical and hematological values in animals. In veterinary medicine such data exist mainly for gentamicin, but for the other members of this group and for the aminocyclitol group there are limited data. The information on ruminants is rather scarce and for goats such experimental results are not available. Comparative investigations of changes in biochemical and hematological parameters after aminoglycoside and aminocyclitol treatment at therapeutic doses

are scarce and our work aims to fill this gap in the knowledge. Since these drugs are used for treatment of infections that also cause changes in some blood biochemical and hematological parameters, if the physician does not take into account the possible alterations caused by aminoglycosides, an incorrect diagnosis may be made and an improper medication could be administered. In this research, the possible changes in blood biochemical and hematological values after aminoglycoside treatment has been studied, and an investigation of the degree of these changes has been performed. Considering the above fact the present investigation has been undertaken with the aims to evaluate the effect of gentamicin on body weight and blood profiles of mice. The results of the present study would, certainly facilitate in understanding the possible hazards of antibiotic on mice, if any, which will help in recommending its judicious use in the field condition of Bangladesh.

MATERIALS AND METHODS

Animals

The mice were purchased from ICDDR, Mohakhali, Dhaka. Before using in the experiment, mice were adapted for 10 days in order to acclimatize them to the environment. The mice were randomly divided into 4 equal groups (n=8). All groups were housed in a compartmentalized rectangular metallic cages (9× 11 ×7 cubic inches) wrapped with wire mesh. The cages were kept in well ventilated room at 28 ±2°C and a relative humidity of 70-80% with natural day and light. The experimental laboratory was cleaned and washed at a regular interval.

Experimental design

Fifty (50) days old 32 male Swiss Albino mice (*Mus musculus*) with an average body weight of 35-40gm were used. The mice were randomly divided into 4 equal groups (n= 8) namely A, B, C, and D. All groups were supplied with standard broiler pellet (4 gm/mice/day) and fresh drinking water was given *ad libitum* throughout the experimental period of 35 days. Group D was kept as control and was fed with normal broiler pellet along with 0.06ml normal saline administered

through intramuscular route daily for up to 10 days. Mice of group A, B and C were maintained as treated groups and administered with 0.12ml, 0.06ml and 0.03ml, respectively of gentamicin sulfate injectable solution through intramuscular route on a daily basis of a 10 day period. Here Pediatric dose of gentamicin was followed (7.5mg/kg B.Wt). Group A (0.12ml gentamicin) considered as high dose, group B (0.06ml gentamicin) as normal dose and lastly, group C (0.03ml gentamicin) as half dose to be compared with the pediatric dose. Several parameters were measured in this study that included body weight, blood biochemistry and serological profile.

Haematological studies

On day 35th of the experiment (at approximately 80 days of age), blood samples were collected by sacrificing the mice. Serum was separated and blood cells were examined for Total erythrocyte count (TEC), Hemoglobin (Hb) content, Total leukocyte count (TLC), Differential leukocyte count (DLC) and Packed cell volume (PCV) as per methods indicated by Lamberg and Rothstein (1977).

Biochemical studies

The biochemical parameters of serum: Level of Triglyceride, serum cholesterol, high density lipoprotein (HDL) and Serum creatinine were determined by the method indicated by Sood (2006).

Statistical analysis

All data were expressed as mean ± SD, and differences among the groups of animals were compared using one-way ANOVA with post-hoc Duncan's test. Paired t- tests were used to compare pre-treatment and post-treatment value of different groups. Statistical significance was set at P < 0.05 and P<0.01. Statistical analysis was performed using SPSS software version 20 (SPSS Inc., Chicago, IL, USA.)

RESULTS AND DISCUSSION

Effects on body weight gain

The impacts of gentamicin administration on body weight of different groups of mice are presented in the Table 1. The mean initial body weight of all groups of mice of approximately 60 days of age (day 0 of experiment) were almost similar (A, B, C and D; 36.93±2.38g, 35.812±2.03g, 36.075±2.83, 36.063±3.78g respectively). The differences between the values were insignificant. The post-treatment body weight differs significantly from their respective pre-treated value.

The body weight showed many variation when it was recorded at the day 5th of the experiment. Group A and D showed significant ($P<0.05$) decrease in body weight (34.125±1.85g, 31.713±3.10g respectively) compared to the day 0 body weight whereas Group B and C showed increase in body weight (38.212±1.99g, 36.40±1.89g respectively). On day 10 all the groups (A, B, C and D) showed increase ($P<0.05$) in the body weight (38.95±1.83g, 38.625±1.50g, 37.612±1.73g and 33.96±1.09g respectively).

Table 1
Effects of gentamicin on weight gain (mean ± SE) in different groups of mice (n=8).

Groups	Body weight (gm) (Mean±SE)		
	Pre treatment	Post treatment	
	Day 0	Day 5	Day10
Group A (high dose)	36.93±2.38	34.12±1.85	38.95±1.83
Group B (Normal dose)	35.812±2.03	38.21±1.99	38.62±1.50
Group C (Half dose)	36.075±2.83	36.40±1.89	37.61±1.73
Control Group	36.063±3.78	31.71±3.10	33.96±1.09
Level of significance	NS	**	**

The obtained data shows no significant changes among the initial body weight of mice at the day 0 of experiment. Although, the data shows decrease in body weight (5th day) in group A and D compared to the day 0 body weight, which runs accordingly to the statement of Qadir et al., (2011) who stated that the body weights decreases significantly after treatment with gentamicin and

Naveed et al., (2013) who showed that gentamicin treated animals loses body weight significantly different from control group animals. Group B and C (5th day, control group included) shows an increase in body weight. On the day 10 all the groups (A, B, C, and D) showed an increase in the bodyweight. This increment in the treated groups might be due to increased feed intake, feed consumption, utilization, digestion, absorption and metabolism of supplied feed nutrient essential for their health and body weight gain. The results obtained coincide with the findings of Manickam et al., (1994), Pradhan et al., (1998), and Islam et al., (2004). Cavazzoni et al., (1998), Rowghani et al., (2007) who stated that mean body weight and daily live weight gain were higher ($P<0.05$) in the gentamicin administered rats than the control group. Another assumption might be, antibiotics when used at a lower dose can act as growth promoter, which in turn enhances the growth performance of the live individual. This statement is similar to that of (Jukes, 1977) who showed in his experiment that low doses of antibiotics also stimulate weight gain in healthy animals fed nutritionally complete feed.

Effects on blood parameters

Effects on total erythrocyte count (TEC)

The effects of gentamicin on total erythrocyte count (TEC) of different groups of mice are presented in the Table 2. Total erythrocyte count (TEC) is higher significantly ($p< 0.01$) in treated group B (7.95±.161) and A (7.73±0.132) than that of control group D (7.43±.299) whereas, the value of group C (7.23±.341) is drastically lower than that of control group.

Effects on total leukocyte count (TLC)

The effects of gentamicin on total leukocyte count (TLC) of different groups of mice are presented in the Table 2. The total leukocyte count (TLC) is lower significantly ($p< 0.01$) in treated group A (7.99±0.11), B (7.81±0.12) and C (7.76±0.35) than that of control group (8.14±.09).

Effects on hemoglobin content (Hb)

The effects of gentamicin on hemoglobin content (Hb) of different groups of mice are described in the Table 2. Here in this table the hemoglobin content in group B (8.05 ± 0.28) and group A (7.80 ± 0.42) are at a higher value compared to the control group (7.50 ± 0.23). On the other hand the value of group C (7.49 ± 0.24) is slightly lower than that of control group.

Effects on Packed cell volume (PCV)

Effects of gentamicin on packed cell volume (PCV) are presented in Table 2. The current data shows significantly higher rate of PCV in group B, A and C ($31 \pm 1.35\%$, $30.33 \pm 1.33\%$ and

$28.03 \pm 1.00\%$ respectively) in comparison with the control group ($28 \pm 1.29\%$).

Effects on differential leukocyte count (DLC)

Effects of gentamicin on differential leukocyte count (DLC) are presented in Table 3. In case of differential leukocyte count (DLC) the percentage of different cells shows great variation amongst the groups as compared to that of control. Percentage of neutrophil and monocyte was recorded the highest in Group B ($34.25 \pm 1.25\%$, $2.25 \pm 0.48\%$ respectively), eosinophil in group A ($3 \pm 1.25\%$) and lymphocyte in group C ($64.67 \pm 1.33\%$).

Table 2
Effects of gentamicin on hematological parameters of different groups of mice (n=8).

Parameters	Mean \pm SE				Level of significance
	Group A	Group B	Group C	Control Group	
TEC(mill/cmm)	7.73 ± 0.132	7.95 ± 0.161	7.23 ± 0.341	7.43 ± 0.299	**
TLC(thousand/cmm)	7.99 ± 0.11	7.81 ± 0.12	7.76 ± 0.35	8.14 ± 0.09	**
Hb(gm/dl)	7.80 ± 0.42	8.05 ± 0.28	7.49 ± 0.24	7.50 ± 0.23	* *
PCV(%)	30.33 ± 1.33	31 ± 1.35	28.03 ± 1.00	28 ± 1.29	**

Table 3
Effects of gentamicin on differential leukocyte count (DLC).

Name of the cell	Neutrophil (%)	Eosinophil (%)	Lymphocyte (%)	Monocyte(%)
Group A	32.67 ± 0.88	3 ± 0.56	63 ± 1.16	1.67 ± 0.88
Group B	34.25 ± 1.3	2.25 ± 0.47	61.75 ± 1.03	2.25 ± 0.48
Group C	33 ± 1.15	2.67 ± 0.33	64.67 ± 1.33	1.33 ± 0.33
Control Group	32.33 ± 0.88	2.00 ± 0.58	62.33 ± 1.76	2.67 ± 0.88
Level of significance	*	**	**	**

In total erythrocyte count (TEC) the results obtained in case of group B and A are somewhat dissimilar according to Elyazji et al., (2013) who assessed that there is a insignificant decrease in RBCs count with a percentage change of -5.62 and -5.62%, respectively compared to controls. The value determined in group C shows similarity with the findings of Nale et al., (2013) who stated that there was significant reduction in TEC levels ($P \leq 0.05$) after gentamicin administration in rats.

In case of total leukocyte count the results obtained in present research are similar to Nale et al., (2013) who stated that there was significant

reduction in TLC level ($P \leq 0.05$) found after gentamicin administration in rats. It also goes similar according to the findings of Elyazji et al., (2013) whose study showed a significant decrease in WBCs count in rabbits injected daily with gentamicin alone for 10 and 20 days.

In hemoglobin estimation the result stated in group A and B is similar to that of Izat et al., (1998) who observed that hemoglobin concentration of blood in mice is enhanced by gentamicin administration. In addition Muzaffar et al., (2003) further stated that gentamicin treatment had better hemoglobin concentration compared with control. The present

result is contradictory to that of Baidya et al., (1994), who observed that administration of antibiotics do not have any influence on the hemoglobin concentration. The result found in group C has is the same to the findings of Nale et al., (2013) who stated that there was significant reduction in hemoglobin concentration ($P \leq 0.05$) found after gentamicin administration in rats.

In case of packed cell volume estimation (PCV) the findings shows dissimilarity with the statement of El Badwi, (2012) according to whom, in gentamicin treated rats the values of PCV were significantly lower than the value estimated in the control group. It also goes similar with the findings of Nale et al., (2013) who explained in his experiment that there was significant reduction in packed cell volume ($P \leq 0.05$) found after gentamicin administration in rats. This however, showed similarity according to Izat et al., (1998) who observed that PCV value of blood in mice is enhanced by gentamicin administration.

In differential leukocyte count the evaluated data shows the same phenomena as stated in the experiment conducted by Baiday et al., (1994) who observed that administration of antibiotics do not have any influence on the differential leukocyte count (DLC). According to Sheikh et al., (2013) there occurs significant increase in lymphocyte count and neutrophil percentage which is similar to the current findings.

Effects on bio-chemical parameters

Effects on serum triglyceride level

Serum triglyceride level (mean \pm SE) in all groups of mice are presented in Table 4. Serum triglyceride of group A, B, C, D are (121.37 \pm 19.28, 211.96 \pm 49.13, 135.25 \pm 29.57, 120.45 \pm 10.04) mg/dl respectively. Significantly ($p < 0.05$) higher level of triglyceride is found in group B compared to all others. Although all the groups (A, B and C) shows values higher than that of control group.

Effects on serum creatinine level

Effects of gentamicin on serum creatinine level are presented in Table 4. The current data shows significantly ($P < 0.01$) high serum creatinine level in group B, A and C (0.454 \pm .06, 0.452 \pm .16 and 0.420 \pm .04 respectively) in comparison with the control group (0.352 \pm .10) gm/dl.

Effects on serum cholesterol level

Effects of gentamicin on serum cholesterol level are presented in Table 4. The total cholesterol level is higher significantly ($p < 0.01$) in treated group B (122.74 \pm 9.37) compared to that of control group D (7.43 \pm .299).

Effects on serum high density lipoprotein (HDL) level

Effects of gentamicin on high density lipoprotein level are presented in Table 4. The current data shows significantly higher rate of HDL in group B, C and A (71.85 \pm 1.98, 47.05 \pm 7.71 and 42.64 \pm 9.38) mg/dl respectively in comparison with the control group (39.18 \pm .93) mg/dl.

Table 4

Effects of gentamicin on biochemical parameter (mean \pm SE) in different groups of mice (n=8).

Parameters	Mean \pm SE				Level of significance
	Group A	Group B	Group C	Control Group	
Triglyceride(mg/dl)	121.37 \pm 19.28	211.96 \pm 49.13	135.25 \pm 29.57	120.45 \pm 10.04	**
Creatinine (mg/dl)	0.452 \pm .16	0.454 \pm .06	0.420 \pm .04	0.352 \pm .10	**
Cholesterol(mg/dl)	87.56 \pm 8.04	122.74 \pm 9.37	94.61 \pm 6.77	109.43 \pm 7.16	**
HDL(mg/dl)	42.64 \pm 9.38	71.85 \pm 1.98	47.05 \pm 7.71	39.18 \pm .93	**

In case of serum triglyceride level the stated data is very effective and most similarly with the finding of Balasinka and Mazur (2004) who reported that gentamicin participate actively in the development of atherosclerosis which is characterized by elevated triglyceride levels in blood plasma. This finding is in agreement with the study of Akter et al., (2013) who found that mice treated with gentamicin showed the significant ($P < 0.01$) increase in blood TG level compared to other (control) groups.

In estimation of serum creatinine level the data shows similarity to that of Elyazji et al., (2013) who stated that a significant increase in serum creatinine occurs in the group injected with gentamicin alone for 10 and 20 days. It is also in accordance with the findings of El Badwi (2012) who stated that the gentamicin treated group scored the higher values of urea, creatinine and total protein when compared to the normal control.

In calculating the serum cholesterol level the obtained data is found similar to the findings of Abu-Spetan et al., (2001) who demonstrated that gentamicin treatment produces significant elevation in the cholesterol level. This finding can also be compared with the study of Akter et al., (2013) who stated that mice treated with gentamicin showed a significant ($P < 0.01$) increase in blood TC level compared to other groups.

In determining high density lipoprotein the obtained data can be compared with the study of Herrington et al., (2000) who reported that gentamicin produced significant increases in HDL levels. This finding is also similar with the study of Akter et al., (2013) who found that mice treated with gentamicin, showed a significant increase in blood HDL level.

CONCLUSION

The results from the present study signifies that administration of gentamicin at pediatric dose (7.5mg/kg B.Wt) has no visible adverse effect on body weight gain, hematological and serological parameters of an individual as the obtained data shows no obvious signs of abnormalities in experimental swiss albino mice (*Mus musculus*). Although normal pediatric dose caused slight

elevation of TEC value, hemoglobin content and packed cell volume (PCV) and also caused mild increase in the serological parameters like serum creatinine, triglyceride, cholesterol and HDL level but no values exceeded the normal range of hematological and serological values. Despite much research has shown that intramuscular administration of gentamicin causes various physiological and pathological alterations which includes severe nephrotoxicity, ototoxicity and gross pathological changes of the infected organs, but only if it is administered at a very high dose and for a prolonged period of time. So according to this research it can be said to some extent that gentamicin if administered at pediatric dose is safe.

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