INTERNATIONAL JOURNAL OF PHARMACEUTICAL, CHEMICAL AND BIOLOGICAL SCIENCES

Available online at www.ijpcbs.com

Research Article

SOME HEMATOLOGICAL AND PHYSIOLOGICAL CHANGES ASSOCIATED WITH GENTAMICIN AND/OR NOVALGIN INJECTION IN RABBITS

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ABSTRACT

Gentamicin is an aminoglycoside antibiotic, used to treat many types of bacterial infections, particularly those caused by Gram-negative organisms. Gentamicin is also ototoxic and nephrotoxic, with this toxicity remaining a major problem in clinical use [1] .The present study is aimed to assess the risk factors, diagnosed hematological and biochemical alterations associated with Gentamicin and/or Novalgin injection in rabbits. Male rabbits were assigned to one of five groups (12 rabbits each) which received subcutaneous injections for 10 and 20 days: Control; (G) Gentamicin alone; (N) Novalgin alone; (G + N) Gentamicin + Novalgin; (G rec) Gentamicin recovery; (N rec) Novalgin recovery and (G + N rec) Gentamicin + Novalgin recovery. In (G rec) and (G + N rec), rabbits recovered for 14 days after the last injection. Upon Gentamicin and/or Novalgin injection, there were a general decrease in RBCs count, Hb content, hematocrit (HCT) value, mean corpuscular hemoglobin (MCH) and WBCs total count. Whereas mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and blood platelets were increased. It is clearly pronounced that Gentamicin and Novalgin injection is more effective in experimental duration of 10 & 20 days. Administration of Gentamicin and/or Novalgin caused significant increase of urea, uric acid, creatinine concentration and ALP activity as compared to control. Whereas, there were a non significant decrease in total protein in animals injected with Gentamicin or Novalgin and decreased significantly in animals injected with Gentamicin and Novalgin. Signs of improvements in hematological parameters urea, uric acid, creatinine and total protein and alkaline phosphatase were noticed after drugs stopped.

Keywords: hematology, biochemistry, Gentamicin , Novalgin, rabbits

INTRODUCTION

Aminoglycosides, such as gentamicin, are a class of clinically important antibiotics used extensively in the treatment of infections, particularly against aerobic gram negative bacteria [2] .

Aminoglycosides can be given once daily despite an elimination half life of two to three hours. Higher serum aminoglycoside concentrations are associated with longer post antibiotic effects and increased bactericidal activity[3] .

Gentamicin is an aminoglycoside antibiotic commonly used in the treatment of life-threatening Gram-negative bacterial infections[4].

Most of the intravenously administered dose is excreted in the urine, whereas some of the aminoglycoside injected is selectively accumulated in the renal cortex leading to renal cell injury[2,5].

The role of the kidney in relation to plasma clearance and maintenance of metabolic homeostasis makes it vulnerable to the toxic effects of drugs. Renal toxicity can be the result of hemodynamic changes, direct cellular or tissular injury, inflammatory tissular injury and/or obstruction of renal excretion[6]. The toxicity of Gentamicin, the

most widely used drug in this category, is believed to be related to the generation of reactive oxygen species (ROS) in the kidney[7]. Most of the intravenously administered dose is excreted in the urine, whereas some of the aminoglycoside injected is selectively accumulated in the renal cortex leading to renal cell injury[2,5]. Gentamicin is also ototoxic and nephrotoxic, with this toxicity remaining a major problem in clinical use[1] . Gentamicin or other aminoglycosides administered as ingredients in cement used for prosthetic joints or used to irrigate wounds are also highly unlikely to cause toxicity[8]. Gentamicin can also be highly nephrotoxic, particularly if multiple doses accumulate over a course of treatment. For this reason gentamicin is usually dosed by body weight. Various formulae exist for calculating gentamicin dosage. Also trough and peak serum levels of gentamicin are monitored during treatment, generally before and after the third dose is infused[9]. The impairment of renal mitochondrial antioxidant system by gentamicin intoxication supports the role of ROS in gentamicin-induced renal damage[10].

Dipyrone or metamezol (Analgin and Novalgin) is the sodium sulfonate of aminophenazone that is widely used as analgesic, antipyretic and anti-inflammatory drug. In Many countries its use is considered justified only in severe pain where no alternative is available or suitable. Dipyrone has been given orally, intramuscularly, intravenously and rectally as suppository[11] .

Agranulocytosis is a rare disease in Brazil, and there was considerable variability in its incidences between different regions[12]. The data that will be available at the conclusion of the LATIN Study will enable definition of the frequency of agranulocytosis in Brazil and other Latin American countries, as well as to what extent dipyrone is associated with its onset. This information essential for defining health policies regarding dipyrone in these countries[13]. In addition, in Spain have assessed association of agranulocytosis with metamizol (dipyrone) in a large data base for the surveillance of blood dyscrasias[14] .

Kidney lesions may induce marked impairments in such functions. Besides, primary renal failure may be associated with arterial hypertension which, in turn , results in arterial lesions and cardiac failure. The present work deals with the effects of Novalgin (an antipyretic) and/or Gentamicin (an antibiotic) on the rabbit's blood[15].

MATERIALS AND METHODS

This study was carried out in July, 2008 at the Department of Biology, Islamic University of Gaza - Palestine.

Experimental Animals

A total number of 66 domestic rabbits weighing 1000-1200gm were used in the present study. Animals were housed 6 to a cage under normal environmental conditions of temperature (22±2^{o}C) and humidity (70%) with an alternating 12-hour light/dark cycle. Animals were supplied with a commercial balanced diet (Anbar 590), and water was provided *ad libitum* daily all over the experimental period of three weeks.

Experimental design

Animals were divided into five groups as follows

The 1st group served as normal control and injected subcutaneously with deionized water daily for 20 days. The 2nd group (n=12) were injected subcutaneously with a daily dose of 50 mg/kg body weight of Gentamicin alone for 10 and 20 days. The 3rd group (n=12) were injected subcutaneously with a daily single dose of 25 mg/kg body weight of Novalgin alone for 10 and 20 days. The 4th group (n=12) were injected subcutaneously with a daily single dose of 25 mg/kg body weight of Novalgin + 50 mg/kg body weight of Gentamicin for 10 and 20 days. The 5th Group "Recovery" recovered for 14 days after the last injection of Gentamicin and/or Novalgin.

Blood sampling and processing

At each sampling date, 6 animals were taken from each group and decapitated. Blood samples were collected into two tubes. The first tube contained EDTA with avoiding first drop for complete blood count

(CBC) analysis. Blood samples in the other tube were left for a short of time to allow clotting. Clear serum samples were obtained by centrifugation at 3000 r.p.m. for 20 min. Clear serum samples were kept in a deep freeze (-18^{o}C) for biochemical analysis. However determination of total proteins and enzymes activity were carried out on fresh serum samples.

I. Physiological Studies

1. Hematological Parameters

Complete blood counts (CBC) in rabbits were obtained by a full-automated Abbott Cell Dyn 1700 Hematology Analyzer. USA, in Al-shifa Hospital Laboratories. The following measurements were carried out, Hemoglobin content (Hb), Total Red blood cells (RBCs) count, Hematocrit value (HCT), Mean corpuscular volume (MCV), Mean corpuscular hemoglobin (MCH), Mean corpuscular hemoglobin concentration (MCHC), Total White Blood Cells (WBCs) count, Platelet count (PLT). Serum was processed for determination of serum creatinine, serum uric acid, serum urea and total protein using commercially available kits of Span Diagnostics Ltd., India [16]. The measurement of serum ALP activity was based on method Boehringer reagent kits were used in the previous enzyme assay[17].

Data analysis

Data were computer analyzed using SPSS 11.0 for windows (Statistical Package for the Social Sciences Inc, Chicago, Illinois). Means were compared by independent – sample-test. Percentage change was also calculated.

RESULTS

I- Hematological parameters

Red Blood Cells (RBCs) Count

Table (1) showed a non significant decrease in RBCs count with a percentage change of -5.62 and -5.62% respectively compared to controls by daily injection of Gentamicin alone for 10 and 20 days . Such decreases were significant after Novalgin alone injection with a percentage change of -10.68 and -12.78%. However injection of Gentamicin +Novalgin for 10 & 20 days showed highly significant decreases of RBCs count with a percentage change of -23.4 and -19.26% respectively. These decreased became non-significant in recovery group of Gentamicin alone and Novalgin alone but still significant in recovery group of Gentamicin + Novalgin group recording -12.36 %.

Hemoglobin (Hb)

In **table (2)**, the changes in Hb content of Gentamicin alone injection was significant decreased of 18.54 and 14.77% after 10 and 20 days, respectively, compared to controls, while to 3.46% in recovery groups. After injection of Novalgin alone, Hb content showed significant decreases of 21.12 and 16.87% after 10 and 20 days, respectively, compared to controls and to 5.89% in recovery group. Whereas, injection of Gentamicin +Novalgin for 10 &20 days showed highly significant decreases of Hb content at rates of 24.77 and 24.50% respectively compared to controls. Even when Gentamicin +Novalgin was stopped, Hb content still decreased non significantly of 8.31%, compared to controls.

Hematocrit (Hct)

Table (3) showed that, Hct was decreased non significantly in animals given Gentamicin alone at rates of 4.49 and 4.45% after 10 and 20 days, respectively, compared to control and 1.92% in recovery group. Animals administered Novalgin alone for10 and 20 days , recorded significant decrease ($P<0.05$) in Hct, at rates of 7.21 and 4.88%, respectively, compared to controls. Subcutaneous injection of Gentamicin + Novalgin for 10 &20 days showed significant decreases of Hct value at rates of 8.4 and 11.7% respectively compared to controls. Upon recovery, Hct still recorded decreases non significantly of 5.32%, compared to controls exhibited levels close to control levels.

MCV , MCH and MCHC

Table (4) showed that, the current investigation of MCV for 10 days were significantly increased concomitant with the changes of RBCs count , Hb content and Hct levels. Whereas, these values were decreased significantly after 20 days post injection with Gentamicin and/or Novalgin in rabbits.On the other hand These changes

still decreased non significantly after recovery in Gentamicin and Novalgin alone and decreased significantly after recovery in Gentamicin + Novalgin.

In table (5) MCH were decreased significantly after 10 days of Gentamicin and/or Novalgin. These changes were non significantly after 20 and in recovery groups, exhibited levels close to control levels.

On the other hand, table (6) showed that, MCHC were increased significantly after 10 days of Gentamicin alone recording 5.94% and 11.30% after Gentamicin + Novalgin together injection and non significantly after Novalgin alone injection. After 20 days of Gentamicin and/or Novalgin injection MCHC were non-significant increased after Gentamicin alone and Novalgin alone injection and significant increased after Gentamicin + Novalgin together injection. Also these increment still recorded non significantly exhibited levels close to control levels.

Platelet count

Table (7) showed that, daily injection of Gentamicin alone for 10 &20 days increased non significantly in PLT count with a percentage change of 6.7 and 8.26% respectively compared to controls. Such increases were also non significant after Novalgin alone injection in rabbits at rates of 2.36 and 4.92% after 10 and 20 days, respectively, but increased significantly in recovery with percentage change of 12.06% compared to controls. However injection of Gentamicin +Novalgin for 10 &20 days showed non-significant increases of PLT count at rates of 1.16 % at 10 days and highly significant increases of PLT count at rates of 23.10% for 20 days compared to controls. These increased still significant in recovery group.

White Blood Cells (WBCs) count

The present study showed a significant decrease in WBCs count in rabbits injected daily with Gentamicin alone for 10 and 20 days with a percentage change of 10.46 and 21.45% respectively compared to controls. These changes were also recorded after Novalgin alone injection in rabbits at rates of 11.12 and 22.09% after 10 and 20 days, respectively, Whereas, injection of Gentamicin +Novalgin for 10 &20 days showed significant decreases of WBCs count at rates of 18.30 and 12.30% respectively compared to controls. Upon recovery, WBCs still recorded highly significant decreases at rates of 19.95, 21.04 and 23.63% in Gentamicin and/ or Novalgin injection compared to controls.

II- Biochemical parameters

Urea

In table (9) there was a significant increase in urea concentration with Gentamicin alone injection for 10 and 20 days recording 10.78% and 13.10% respectively . Such increases were non-significant after Novalgin alone injection in rabbits after 10 days and significant increased with 11.19% percentage change after 20 days .However injection of Gentamicin +Novalgin for 10 &20 days showed a highly significant increases of urea concentration with 22.62% and 24.19% percentage change respectively. These changes still increased significantly in recovery groups of Novalgin injection ,and Gentamicin +Novalgin injection.

Uric acid

Uric acid concentration in the serum of treated rabbits were shown in table (10) in which it increased significantly in response to daily injection of Gentamicin alone and Gentamicin + Novalgin together and significant in Novalgin alone for 10 days. These increment still increased highly significant in Gentamicin and/or Novalgin recording 29.76, 28.57 and 30.71% respectively. These increment still increased highly significant in recovery groups in Gentamicin and/or Novalgin.

Creatinine

Table (11) showed a significant increase in serum creatinine in the group injected with Gentamicin alone for 10 and 20 days recording 1.63 and 1.79 mg/dl respectively compared to controls. Similar changes was showed in the group injected with Novalgin alone for 10 and 20 days recording 1.61 and 1.65 mg/dl respectively compared to controls. Also, injection of Gentamicin +Novalgin for 10 &20 days showed a

significant increases of creatinine concentration with percentage change of 40.68 and highly significant increases 55.83% respectively compared to controls. These changes still increased significantly in recovery groups of injection of Gentamicin and/or Novalgin.

Total protein

Data in Table (12) showed that injection of Gentamicin alone and Novalgin alone for 10 and 20 days induced non significant decreased of total proteins. These changes increased significantly in Gentamicin +Novalgin injection for 10 &20 days, and in recovery groups of Gentamicin + Novalgin recording-17.45, -13.79 and -10.31% respectively.

Alkaline phosphatase (ALP) enzyme

Table (13) showed a non significant increase in serum ALP in the group injected with Gentamicin alone and Novalgin alone for 10 days recording 8.75 and 4.76 % of change; and 22.9 and 20.58% of change respectively after 20 days compared to controls. These changes decreased non significantly in recovery groups of Gentamicin alone (-6.97%); significantly in Novalgin alone injection (-10.70%); ,and increased highly significant in Gentamicin +Novalgin injection (10.72%).

Table 1: Effect of Daily injection of Gentamicin and/or Novalgin on RBC count (X10⁶ cell/µl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	5.3±0.42	Mean ± S.E % of change	5.04±0.04 -5.62	4.77±0.10* -10.68	4.11±0.12** -23.4
20 days	5.87±0.39	Mean ± S.E % of change	4.95±0.10 -5.62	5.12±0.26* -12.78	4.74±0.22** -19.26
Recovery	5.26±0.36	Mean ± S.E % of change	5.07±0.31 -3.60	5.01±0.28 -4.75	4.61±0.21* -12.36

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant.

Table 2: Effect of Daily injection of Gentamicin and/ or Novalgin on HBG (g/dl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	13.97 ± 0.70	Mean ± S.E % of change	11.38±0.09* -18.54	11.02 ± 0.21* -21.12	10.51 ±0.11** -24.77
20 days	12.33 ± 0.41	Mean ± S.E % of change	10.51±0.63* -14.77	10.25 ± 0.38* -16.87	9.31 ±0.26** -24.50
Recovery	11.55 ± 0.36	Mean ± S.E % of change	11.15±0.51 -3.46	10.87 ± 0.38 -5.89	10.59 ±0.69 -8.31

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant.

Table 3: Effect of Daily injection of Gentamicin and/or Novalgin on HCT (%) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	34.54±0.90	Mean ± S.E % of change	32.75±0.51 -4.94	32.05±0.61* -7.210	31.64±0.33* -8.40
20 days	39.60±0.36	Mean ± S.E % of change	37.84±0.58 -4.45	37.67±0.50* -4.88	34.97±0.66** -11.70
Recovery	34.40±0.38	Mean ± S.E % of change	33.74±0.30 -1.92	32.07±0.18 -6.70	32.57±0.26 -5.32

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant.

Table 4: Effect of Daily injection of Gentamicin and/or Novalgin on MCV (µm3) of rabbits among control and experimental groups for 10,20 days and recovery.

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	56.71±0.33	Mean ± S.E % of change	65.01±0.35* 14.6	62.88±0.95* 10.87	76.98±0.60* 35.7
20 days	70.54±0.32	Mean ± S.E % of change	63.87±0.30 -9.46	63.15±0.80* -7.61	59.94±0.71* -15.03
Recovery	62.08±0.11	Mean ± S.E % of change	58.18±0.21 -6.22	57.00±0.31 -8.18	56.30±0.26* -9.31

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant.

Table 5: Effect of Daily injection of Gentamicin and/or Novalgin on MCH (Pg) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	23.01±0.32	Mean ± S.E % of change	22.2±0.28** -30.53	21.87±0.21* -4.96	25.57±0.26* 11.30
20 days	22.35±0.25	Mean ± S.E % of change	21.15±0.39 -5.37	20.58±0.27 -7.92	20.58±0.27 -7.92
Recovery	21.88±0.21	Mean ± S.E % of change	21.20±0.61 -3.11	20.3±0.49 -3.88	21.11±0.55 -3.52

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 6: Effect of Daily injection of Gentamicin and/or Novalgin on MCHC (%) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	29.8±0.39	Mean ± S.E % of change	31.57±0.26* 5.94	30.37±0.36 1.91	33.17±0.28* 11.30
20 days	33.31±0.40	Mean ± S.E % of change	36.15±0.38 8.53	34.71±0.76 4.20	36.97±0.60* 10.98
Recovery	29.68±0.41	Mean ± S.E % of change	31.74±0.26 6.94	30.87±0.29 4.00	33.3±0.22* 12.20

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 7: Effect of Daily injection of Gentamicin and/or Novalgin on PLT (X10³ /µl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	443.84±25.3	Mean ± S.E % of change	473.5±30.6 6.7	454.3±39.20 2.36	449.0±21.5 1.16
20 days	411.17±19.33	Mean ± S.E % of change	445.17±25.3 8.26	430.17±19.6 4.92	506.17±18.2** 23.10
Recovery	423.0±22.15	Mean ± S.E % of change	474.7±26.6* 12.22	474.0±31.77* 12.06	504.4±30.26* 12.24

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 8:Effect of Daily injection of Gentamicin and/or Novalgin on WBC (X10³ cell/µl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	7.59±0.25	Mean ± S.E % of change	4.11±0.33* -10.46	4.08±0.26* -11.12	3.75±0.38* -18.30
20 days	7.88±0.36	Mean ± S.E % of change	6.19±0.30** -21.45	6.14±0.25** -22.09	6.91±0.22* -12.30
Recovery	7.32±0.41	Mean ± S.E % of change	5.86±0.33* -19.95	5.78±0.26** -21.04	5.59±0.36** -23.63

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 9: Effect of Daily injection of Gentamicin and/or Novalgin on Urea (mg/dl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	48.9±2.55	Mean ± S.E % of change	54.17±2.28* 10.78	53.17±1.95 8.73	59.96±2.2** 22.62
20 days	49.6±2.16	Mean ± S.E % of change	56.10±2.11* 13.10	55.15±1.77* 11.19	61.6±2.19** 24.19
Recovery	48.6±1.70	Mean ± S.E % of change	52.15±1.60 7.30	53.66±1.77* 10.41	60.6±3.11** 24.69

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 10: Effect of Daily injection of Gentamicin and/or Novalgin on Uric Acid (mg/dl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	4.19±0.05	Mean ± S.E % of change	5.41±0.11* 29.12	5.35±0.10 27.68	5.45±0.13** 30.07
20 days	4.20±0.04	Mean ± S.E % of change	5.45±0.06** 29.76	5.40±0.06** 28.57	5.49±0.05** 30.71
Recovery	4.37±0.03	Mean ± S.E % of change	5.39±0.06** 23.34	5.31±0.03** 21.51	5.43±0.03** 24.26

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 11: Effect of Daily injection of Gentamicin and/or Novalgin on Creatinine (mg/dl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	1.18 ± 0.03	Mean ± S.E % of change	1.63±0.02* 38.14	1.61 ± 0.04* 36.44	1.66 ±0.03* 40.68
20 days	1.2 ± 0.03	Mean ± S.E % of change	1.79±0.03** 49.17	1.65 ±0.03* 37.5	1.87 ± 0.07** 55.83
Recovery	1.17 ± 0.08	Mean ± S.E % of change	1.59±0.03* 35.90	1.51 ±0.06* 29.06	1.61 ± 0.04* 37.61

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 12: Effect of Daily injection of Gentamicin and/or Novalgin on Total protein (g/dl) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	5.56±0.07	Mean ± S.E % of change	5.11±0.08 -8.09	5.21±0.04 -6.29	4.59±0.06* -17.45
20 days	5.51±0.06	Mean ± S.E % of change	5.00±0.06 -9.26	5.19±0.05 -5.81	4.75±0.03* -13.79
Recovery	5.53±0.05	Mean ± S.E % of change	5.13±0.04 -7.23	5.17±0.06 -6.51	4.96±0.07* -10.31

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

Table 13:Effects of Daily injection of Gentamicin and/or Novalgin on Alkaline phosphatase (IU/ml) of rabbits among control and experimental groups for 10,20 days and recovery

	Control		Gentamicin (G)	Novalgin (N)	Gentamicin + Novalgin(G+ N)
10 days	125.17±0.97	Mean ± S.E % of change	136.12±0.56 8.75	131.13±0.66 4.76	151.15±0.53* 20.76
20 days	131.13±0.66	Mean ± S.E % of change	161.16±0.66* 22.9	158.11±0.22* 20.58	170.0±0.22** 29.64
Recovery	130.19±0.61	Mean ± S.E % of change	121.12±0.22 -6.97	116.26±0.30* -10.70	144.14±0.31** 10.72

SE: Standard error; *P<0.05 significant; **P<0.01 highly significant

DISCUSSION

Hematological constituents usually reflect the physiological responsiveness of the animal to its external and internal environments and this is serving as a veritable tool for monitoring animal health[18].

The effect of Gentamicin and/or Novalgin on Hb content was parallel to its action on RBC count. These changes may be correlated with some pathological changes that developed in blood forming organs with destruction of a number of red cells due to lytic substances or with both factors . In this region the anemia results from hemodilution extra vascular hemolysis as well as from toxic dyshematopoiesis drugs resulted decreased (WBCs and RBCs values attributed to depression of cardiovascular function[19].

Urea is the principal end product of protein catabolism. In general Gentamicin and/or Novalgin injection raised-up the concentration of urea and creatinine in rabbit's blood serum. Enhanced protein catabolism and accelerated amino acid deamination for gluconeogensis is probably an acceptable postulate to interpret the elevated levels of urea. The presence of some toxic compounds might increase blood urea and decrease plasma protein[20] . In addition, an increase in urea concentration suggested that animals experienced hemoconcentration due to animal dehydration .

Uric acid is the end product of the catabolism of tissue nucleic acid, i.e. Purine and pyrimidine bases metabolism[21].The present study demonstrate that the concentration of uric acid in the serum of treated rabbits increased significantly in response to the daily injection of Gentamicin and /or Novalgin. These increment may be due to degradation of purines and pyrimidines or to an increase of uric acid level by either overproduction or inability of excretion.

Significant increase in serum creatinine was also noticed in the group injected with Gentamicin and /or Novalgin. These changes still increased significantly in recovery groups of injection of Gentamicin and/or Novalgin. These results were in accords with previous works[9,22]. These changes may be related to as a decrease in glomerular filtration, with a diminution in diuresis. These results agree with previous works.

The present data showed that injection of Gentamicin and/or Novalgin induced progressive decreased of the total proteins. This decrease is agree with that indicated, serum total proteins and albumin decreased in chicks given 20 mg/kg and higher doses of gentamicin[23]. The antibiotic erythromycin inhibits protein synthesis by binding to 50S ribosomal subunits of sensitive microorgamisms[24]. Cycloheximide is a potent protein synthesis inhibitor causing a slowing down of the movement of ribosomes with respect to the mRNA strand after the ribosomes have been attached to it . This was confirmed by [25,26]. Serum creatinine, uric acid, and urea were found to be significantly increased in rabbits treated with Gentamicin and /or Novalgin. The results support the importance of monitoring serum biochemical parameters when treating with Gentamicin and/or Novalgin. The liver cells play an important role in both synthesis and secretion of ALP into bile. The specific location of the ALP enzyme within both sinusoidal and bile canalicular membranes accounts for the more predominant elevations in certain disorders[27] as

observed in the present study with Gentamicin and /or Novalgin administration. Acute cell necrosis liberates ALP in the circulation and sever enzyme level is elevated.

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