Kafrelsheikh Vet. Med. J. Vol. 6 No. 2 (2008) (298-324)

SOME ADVERSE EFFECTS OF INTERACTION BETWEEN FUROSEMIDE AND ENROFLAXACIN IN ALBINO RATS

Asharaf A. El-Ghoneimy[1]; Shaheen, H.M.[1]; Mouchira M. Mohi[2]; El-Sheikh, W.M.[3] and Ramadan, TM.[4]

[1]Dept. of pharmacology, Fac. Vet. Med., South Valley University (Qena).

[2]Dept. of pharmacology, Fac. Vet. Med., South Valley University (Qena).

[3]Dept. of pharmacology, Animal Health Research Institute, Tanta provincial lab.

[4]Dept. of clinical pathology, Fac. Vet. Med., Sue Fac. Vet. Med., South Valley University (Qena)z canal University .

ABSTRACT

Concurrent administration of both antibiotics and diuretics is more frequently common in animals in acute severe infection when a rapid onset of diuresis is desired or in animal treated for odema. Our studies, were established six groups (N= 10) of albino rats. One group (gp.) was kept as control. The remaining groups were injected intramuscularly (i.m.) with enrofloxacin 10 mg kg^{-1} daily for 5 successive days (gp.2) or furosemide 20 mg kg^{-1} for 3 days at 1^{st} , 3^{rd} and 5^{th} day (gp.6) or combination of both enrofloxacin10 mg kg^{-1} for 5 successive days and furosemide 20 mg kg^{-1} at 1^{st} day (gp.3), 1^{st} and 3^{rd} day (gp.4) and 1^{st}, 3^{rd} and 5^{th} day (gp. 5). Five rats from each group were sacrificed at 2^{nd} and 9^{th} day post-cessation (d p.c.) of treatment. Two blood samples were collected from each animal, for hematological and biochemical parameters. The sacrificed rats were dissected and samples from kidneys, liver, heart, spleen and testes were collected for histopathological examination. The obtained hematological results

revealed a significant decrease in erythrocytic count and hemoglobin concentration, PCV %, MCV, MCH and MCHC % in all treated groups. The effect is more serious in rats treated concomitantly with both enrofloxacin and furosemide particularly rats in gps. 4 and 5. The obtained biochemical findings displayed a significant increase in serum ALT, AST, creatinine and uric acid levels in all treated groups. The effect is more direful in enrofloxacin and furosemide treated gps (3, 4& 5). Moreover, the obtained biochemical data evidenced a significant increase in blood glucose level in gps. (3, 4, 5& 6). Moreover, there were significant decreases in total protein and albumin levels in gp. 5. The histopathological examination divulged mild to severe hemorrhage, with necrosis in myocardium of gps (5& 6), Thickening in the pericardium with fibrinous tissues proliferation in gp. 5, telangiectasias in the blood sinusoids surrounded with aggregations of inflammatory cells, in addition to, vacuolar and hydropic degenerations with necrosis in some of the hepatic cells of most rats in both gps. (4& 5), severe congestion in blood sinusoids with depletion in lymphocytes in white pulp in spleen, gps (3, 4& 5), edema in bowman's capsule led to contraction and disappeared in the glomeruli in kidneys in most rats of gps (4, 5& 6), additionally, albumin casts in the lumen of collecting tubules in gps (5& 6). Moreover, thickening and edema in the wall of blood vessels, beside perivascular aggregation of inflammatory cells particularly in gps (4& 5). Destruction and edema among the semineferous tubules beside degeneration and necrosis in the spermatogonial cells in testes in all groups, disappearance in the sperm inside semineferous tubules gp. (5).

INTRODUCTION

The fluoroquinolones are a class of compounds that comprise a large extending group of synthetic antimicrobial agents. Structurally, all a fluoroquinolones contain a fluorine molecule at the 6-position of basic quinolone nucleus. Despite the basic similarity in the core structure of these molecules, their physiochemical properties, pharmacokinetic characters and microbial activities can vary markedly across compounds. The first of the fluoroquinolones approved for use in animal in the late 1980 s ***(Martinez et al., 2006).***

Enrofloxacin is a synthetic analogue of fluoroquinolones that is markedly for use in veterinary medicine. It is rapidly bactericidal against a broad spectrum of anaerobic bacteria, including strains that are resistant to many other antimicrobial agents. It is also effective against some gram positive bacteria, mycoplasma, and some rickettsial organisms ***(Scheer, 1987; Vancutsem et al., 1990; Walker et al., 1992 and Elsheikh et al., 2002).***

Furosemide (4-chloro-N-[2-furymethyl]-5-sulfamoylanthranilic acid) is a rapidly acting high-ceiling diuretic, which is also known as a loop diuretic ***(KirkendallandStein, 1968).***

Antibiotics and diuretics are frequently used concomitantly in animals in acute severe infection when a rapid onset of diuresis is desired or in animal treated for edema ***(Fahim, 2005)***. The co-administration of several drugs often results in unpredictable therapeutic outcome. Often it is either diminished therapeutic efficacy or increased toxicity of one or more of the administered drugs ***(Rahal et al., 2007).*** This may be attributable to interaction that occurs within the body which may be of pharmacokinetic or pharmaco-dynamic type. Fluoroquinolones

have various kinds of adverse reactions and drug-drug interactions which represented by gastrointestinal disturbances such as nausea, vomiting and diarrhea ***(Martinez et al., 2006).*** As Furosemide, was known to alter the kinetics of some new fluoroquinolones, decreasing the total and renal excretion of lomefloxacin in man ***(Sudoh et al., 1994).***

Therefore, the objective of the present study was to investigate the adverse effects of Enrofloxacin with furosemide-treated rats by determination of some hematological and biochemical parameters as well as the histopathological profile of some of internal organs.

MATERIAL AND METHODS

A) Drugs:-

1- Enrofloxacin: Enrofloxacin (Spectramam-Vet)®, injectable 10% solution. Amoun Pharmaceutical Industries Co., El-salam city, Cairo, Egypt. Enrofloxacin was administered i.m. in a dose of 10 mg kg^{-1} ***(Amer and El-Shaieb, 1998).***

2- Furosemide: (Lasix) ®, Hoochest AG., Frankfurt, Germany. Lasix was administered i.m. in a dose of 20 mg kg^{-1} ***(Briukhanov et al., 2007).***

B) Animals:-

Sixty mature male albino rats (Rattus norvegicus) weighing (200-287 g) obtained from Laboratory Animal House, Faculty of Veterinary Medicine. Zagazig University were used. The rats were kept under hygienic conditions, housed in metal cages containing wood shavings as bedding materials fed on balanced ration and watered ad-libitum. They were accommodated to the laboratory conditions, 2 weeks before being experimented.

Experimental design were demonstrated in table (1):

The rats in all experimental groups were monitored daily for clinical signs. At the 2nd and 9th day post-cessation of treatment, 5 rats from each group were sacrificed. Two blood samples were collected from each animal. one received in test tubes containing EDTA as anticoagulant (for hematological studies), and the other one was centrifuged at 3000 rpm for 15 minutes without any anticoagulant (for serum collection) for biochemical analysis, the serum was collected and kept frozen. After collection of blood samples, the rats were dissected and samples from heart, kidney, liver, lung, spleen and testes were obtained for histopathological examination

Table(1): the experimental design.

Groups	No. of animal / group	Drugs dosage and period of treatment										Time of blood sampling and scarification
		Enrofloxacin (10 mg / kg) per day					Furosemide (20 mg / kg) per day					
		1st day	2nd day	3rd day	4th day	5th day	1st day	2nd day	3rd day	4th day	5th day	
1	10	-	-	-	-	-	-	-	-	-	-	At the 2nd and 9th days post cessation of treatment
2	10	+	+	+	+	+	-	-	-	-	-	
3	10	+	+	+	+	+	+	-	-	-	-	
4	10	+	+	+	+	+	+	-	+	-	-	
5	10	+	+	+	+	+	+	-	+	-	+	
6	10	-	-	-	-	-	+	-	+	-	+	

N.B. furosemide was injected one hour just prior to enrofloxacin injection.

C) Analysis:

1- Biochemical analysis:

Serum samples were used for determination of total proteins ***(King and wooton, 1982)***. albumin ***(Gassbaro et al., 1972)***, glucose ***(Trinder, 1969)***, uric acid ***(Henry et al., 1974)***, creatinine ***(Young et al., 1975)***, GPT [ALT] and GOT [AST] ***(Reitman and Frankel, 1957)***.

2- Hematological analysis:

The hematological parameters (RBCs and WBCs counts, Hb (hemoglobin) % and PCV (packed cell volume) %) were determined according to ***(Dacie and Lewis, 1994)***. Blood indices were calculated using these equations;

- Mean cell volume (MCV) = PCV % / (RBCs X 106) X 100 f
- Mean cell hemoglobin (MCH) = Hb (gm/dl) / RBCs X 106X 10 pg/cell
- Mean cell hemoglobin concentration (MCHC) = Hb (gm/dl) / PCV% X 100 gm/dl

3- Histopathological technique:

Specimens from the internal organs mainly liver, kidneys, heart, spleen and testicles were taken and fixed in 10% buffered formalin. Fixed tissues were processed by routine histopathological procedures, and embedded in paraffin wax. Tissue sections were stained with H&E and examined under the light microscope ***(Bancroft et al., 1990)***.

4- Statistical analysis:

The results were reported as the mean ± S.E., and statistical significance was determined using analysis of variance according to (Snedcor and Cochran, 1982). Means were compared by least significance difference (LSD) test 0.5 significance level ***(Steel and Torrie, 1980).***

RESULTS AND DISCUSSION

Hematological findings:-

The results obtained regarding the effect of Enrofloxacin and/or Furosemide on hemogram and blood indices of treated rats are summarized in table (2 & 3).

It was clarified that, the rats in the gp.2, which treated with enrofloxacin alone for 5 days, evoked a significant decrease ($p < 0.05$) in erythrocytic count at 2nd (d. p.c) hemoglobin concentration (Hb %), packed cell volume (PCV %), at 2nd & 9th (d p.c.) and MCH % at 2nd & 9th (d p.c.), MCHC% at 9th (d p.c.) and MCV at 2nd (d p.c.) compared with the control.

The rats in the gp.3, which treated with combination of enrofloxacin for 5 days and furosemide for one day, revealed significant decrease ($p < 0.05$) in RBCs count, Hb %, PCV%, MCV, MCH %, at 2nd & 9th (d p.c.) and MCHC at 9th (d p.c.) compared with the control. Meanwhile, non significant changes were detected in RBCs count, PCV% & MCH% at 2nd (d p.c.) and MCHC % at 2nd & 9th (d p.c.) compared with gp.2.

The rats in the gp.4, which treated with combination of enrofloxacin for 5 days and furosemide for two days(1st and 3rd day), showed a significant decrease ($p < 0.05$) in RBCs count, Hb %, PCV %, MCV, MCH at 2nd & 9th (d p.c.) compared with the control. Whereas, compared with gp.2, RBCs count, Hb % and PCV % were significantly ($p < 0.05$) decreasedl at 2nd & 9th (d p.c.).

The rats in the gp.5, which treated with combination of enrofloxacin for 5 days and furosemide for three days, displayed a significant decrease ($p < 0.05$) in RBCs count, Hb %, PCV % and MCH % at 2nd & 9th (d p.c.) compared with both the control and gp.2.

The rats in the gp.6, which treated with furosemide alone for 3 days, divulged a significant decrease ($p < 0.05$) in RBCs count, Hb %, PCV %, MCV and MCH % at 2nd & 9th (d p.c.) compared with the

control. In contrast, this group showed a non significant change in RBCs count, Hb %, MCV and MCH %, at 2nd & 9th (d p.c.) compared with gps.(3, 4& 5). Moreover, it provoked non significant change in Hb % and PCV %, at 9th (d p.c.) compared with gps (4&5) respectively.

Analysis of hematological parameters can be beneficial in assessing animal health, as the hemogram and blood indices reflect the statement of the animal. Generally, it was found that, enrofloxacin and/or furosemide significantly causes a reduction in RBCs count, Hb level of treated rats, this reduction is more pronounced in groups (3, 4&5). The anemia induced might be due to inhibition of hemopoiesis, which confirmed by depletion in the lymphocytes in spleen in gps (3, 4& 5). Our results were in accordance with ***(Amer and EL-Shaieb, 1998)*** who mentioned that, i.m. injection of rabbits with enrofloxacin at a dose level of 10 mg kg^{-1} for 5 successive days induced a significant ($p < 0.05$) decrease in erythrocytic count, Hb concentration, PCV %, MCV and MCH %. Moreover, the distirbance in hemogram and hematological indices might be due to disturbance in composition of body fluids ***(Altreuther, 1987)*** or due to disturbance in electrolyte balance induced by excessive vomition and diarrhea ***(Halkin, 1988 and John, 1991).*** Unfortunately, our data cannot provide us with a ready explanation for furosemide induced anemia in group 6. It is worthwhile to contemplate proposals that enlighten us with a proper explanation. The anemia may be due to alteration of hemopoiesis as a result of hepatic pathological lesion or might be due to reduction in bile salts in the small intestine since bile acids are necessary for reduction of ferric ions to ferrous easily absorbed ***(Kaneko et al., 1997).***

In the glow of the previous explanations, one could attribute this furosemide induced anemia to inhibition of hemopoiesis caused by hepatic lesions. This suggestion confirmed by the degenerative changes in the hepatic cells in the present study. Our findings fit in with those reported by ***(Sanofi-Aventis, 2007)*** who recorded that anemia, thrombocytopenia as well as agranulocytosis, aplastic and hemolytic anemias may be occurred as adverse effects accompanied the use of furosemide. Concern regarding anemia induced by concurrent use of both enrofloxacin and furosemide (gp. 3, 4 and 5), undoubtedly, our obtained findings provide us with a ready explanation and needless to say this could be attributable to augmenting effect of both drugs which become greatest in gps 4 and 5.

Biochemical findings:-

The results concerning tested serum parameters are presented in tables (4 and 5).

It was cleared that i.m. injection of rats at a dose level of Enrofloxacin 10 mg kg^{-1} daily for 5 successive days divulged a significant ($p < 0.05$) increase in serum ALT, AST and creatinine at 2^{nd} and 9^{th} (d p.c.) and uric acid at 2^{nd} (d p.c.), meanwhile, non significant changes were evident in total protein, albumin, globulin and glucose at 2^{nd} and 9^{th} (d p.c.) and uric acid at 9^{th} (d p.c.). Increase in serum ALT and AST activities depending on hepatocellular damage ***(San Martin-Nunez et al., 1988).*** Our findings seem conceivable to be attributed to disturbances liver functions resulted from the use of the drug. These results coincide with those previously recorded by ***(Gellert et al., 1981 and Hillel, 1988)*** who stated that administration of enrofloxacin to rats at therapeutic dose resulted in an increase in liver enzymes. The results are

also consistent with those obtained by ***Kobayashi (1985)*** who noted that, there were mild and reversible elevations in serum AST and ALT. Additionally, our results are confirmed by ***Helal et al.,(1995); Ibrahim (1995); Ramadan (1996); Khodary and El-Sayed (1997); Abd El-Alim et al., (2000) and Rasha (2008).*** Moreover, these results were supported by the histopathological studies of hepatic tissues of treated rats which revealed degenerative changes in the hepatic cells and acute toxic hepatitis. The significant ($p < 0.05$) increase in creatinine and uric acid seen conceivable to be attributed to disturbances in kidneys functions as a result of glomerular damage caused by direct effect of enrofloxacin or its metabolite on kidney.

This explanation confirmed by the obtained histopathological alterations in the kidneys in this study. These results are in accordance with ***Khodary and El-Sayed, (1997)***, they reported that enrofloxacin induced a significant increase in creatinine and uric acid in ducklings. Also, the results are in agreement with ***Abd El-Alim et al.,(2000)*** who reported that, ofloxacin administration to chickens at a dose level of 50 and 100 mg / liter or drinking water evoked a significant increase in serum creatinine and uric acid levels. More recently these findings are fit in with those reported by ***Rasha (2008)*** who noticed that Enrofloxacin treated chicks showed a significant increase in serum uric acid allover the experiment. The non significant change in serum total proteins, albumin, globulins seem to coincide with ***(Amer and EL-Shaieb, 1998); Elen (1999); Abd El-Alim et al.,(2000) and Uyanik et al.,(2000).***

Rats treated with Furosemid (gp. 6), displayed a significant ($p < 0.05$) increase in serum ALT, AST and creatinine levels at 2nd and 9th d p.c. and uric acid at 2nd d p.c.. These data seem to be attributable to

disturbances in both liver and kidneys functions owing to the use of Furosemide. The levels of serum ALT, AST increased following liver damage ***(Doxy, 1971)***, accordingly this findings might be attributed to damage of hepatic cells by direct effect of the drug or its metabolites resulting in escape of these enzymes into the plasma. This suggestion was supported by the obtained results of histopathological examination of hepatic tissues of treated rats which revealed hepatic damage and toxic hepatitis. Furthermore, this suggestion was confirmed by ***Butler et al., (2006) and Daniel et al., (2007)*** they identified a novel cytochrome p 450 dependent metabolic pathway in vivo for Furosemide with the formation of chemically reactive cytotoxic metabolite (7- ketocarboxylic acid) via furan epioxidation resulting in cytotoxic effect in both rat and mouth hepatocytes. Moreover these findings come in agreement with ***Sanofi-Aventis, (2007)*** who reported increase in liver transaminases associated with Furosemide treatment.

Regarding the significance increase in creatinine and uric acid levels as a result of a Furosemide treatmen, these results appeared to be attributed to disturbances in the kidney functions. Such findings were supported by the histopathological studies of kidney tissues of treated rats which revealed renal damage detected by a casts in the distal tubules. These results were compatible with those recorded by ***Hori et al., (2000)*** they stated that, rats treated with Furosemide elicited an elevation in creatinine and blood urea nitrogen which associated with degeneration in proximal convoluted tubules. Moreover, similar findings were recorded by ***Sanofi-Aventis, (2007)***, who reported a transient increase in serum creatinine and uric acid levels during Furosemide treatment.

Rats treated with Furosemide elicited a significant ($p < 0.05$) increase in blood glucose level at 2nd and 9th (d p.c.) as compared with control and other compared groups. Our data are in harmony with that presented by ***Dimitriadis et al., (1988)*** and ***Dimitriadis et al., (1998)*** they concluded that prolonged administration of furosemide in vivo, can lead to progressive accumulation of the drug in skeletal muscle which quantitatively most important for glucose disposal in response to insulin in this tissue, furosemide impairs the sensitivity of glucose utilization to insulin in skeletal muscle by directly inhibiting the glucose transport process.

Rats in gp. (3) elicited a significant ($p < 0.05$) increase in serum ALT, AST and creatinine at 2nd and 9th (d p.c.) and uric acid at 2nd (d p.c.) as compared with control group. On the other side, there were non significant changes in serum ALT and AST at 2nd d p.c., uric acid and blood glucose levels at 9th (d p.c.), beside a significant ($p < 0.05$) increase in creatinine at 2nd and 9th (d p.c.), uric acid and blood glucose levels at 2nd (d p.c.) as compared with gp. (2), but in comparison with gp. (6), significant ($p < 0.05$) increase in serum ALT, AST and creatinine levels at 2nd and 9th (d p.c.) were detected.

Rats in gp. (4) evoked a significant ($p < 0.05$) increase in serum ALT, AST, creatinine, uric acid and blood glucose levels at 2nd and 9th (d p.c.), as compared with gps (1, 2& 6).

Rats in gp. (5) provoked a significant ($p < 0.05$) increase in serum ALT, AST, creatinine and uric acid levels at 2nd and 9th (d p.c.) as compared with gps (1, 2& 6). In contrast, there was a significant ($p < 0.05$) decrease in total protein and albumin as compared with control and all other treated groups. Concern regarding the obtained results with gps

(3, 4& 5), there were no available literatures explain the therapeutic outcome of concurrent use of both enrofloxacin and furosemide but, undoubtedly, the co-administration of several drugs often results in unpredictable therapeutic outcome, often it is either diminished therapeutic efficacy or increased toxicity of one of the administrated drugs ***(Rahal et al., 2007).*** This may be attributable to interactions that occur within the body which might be of pharmacokinetic or pharmacodynamic type. Furosemide was known to alter kinetics of some new fluoroquinolones, decreasing the total and renal excretion of lomefloxacin in man ***(Sudoh et al., 1994)*** and difloxacin in goat ***(Fahim, 2005)*** accordingly this prolonging the duration of action and consequently increasing the incidence of more averse effects.

In the glow of the previous notion, one could attribute such obtained data to augmented effect of both drugs or might be owing to delayed renal excretion with consequent prolonged duration and more adverse effects.

Histopathological findings:-

All treated groups showed emaciation except those in the gp. (2) were apparently normal. Enlargement in the internal organs (mainly spleen, liver and heart) with dark in the color were evident in the sacrificed rats, gps (4, 5& 6), at 2^{nd} & 9^{th} (d p.c.), meanwhile no signs were recorded in the kidneys and testicles in all groups. No obvious lesions were detected in scarified rats in gps (2 & 3).

In histopathological observations, the heart in gps (5& 6) showed mild to severe hemorrhage (Fig.1), with necrosis and destruction in myocardium, at 2^{nd} & 9^{th} (d p.c.) Thickening in the pericardium with

fibrinous tissues proliferation were detected in gp. 5, at 9th (d p.c.) (Fig.2). Liver of most rats in both gps. (4& 5) at 2nd & 9th (d p.c.) displayed a telangectiasis in the blood sinusoids surrounded with aggregations of inflammatory cells, in addition to, vacuolar and hydropic degenerations with necrosis and destruction in some of the hepatic cells (Fig.3). Spleen displayed severe congestion in blood sinusoids with depletion in lymphocytes in white pulp, gps (3, 4& 5), at 9th (d p.c.) (Fig.4). Kidneys in most rats of gps (4, 5& 6) at 9th (d p.c.) suffered from edema in bowman's space led to contraction and disappeared in the glomeruli (Fig.5). The kidneys showed albumin casts in the lumen of collecting tubules in the medulla, gps (5& 6), at 9th (d p.c.) (Fig. 6). Otherwise, thickening and edema were showed in the wall of blood vessels, beside perivascular aggregation of inflammatory cells particularly in gps (4& 5) at 9th (d p.c.) (Fig. 7). Testes in most groups displayed destruction and edema in semineferous tubules. Among the semineferous tubules showed edema beside degeneration and necrosis in the spermatogenesis in the rats in all groups at 2nd and 9th (d p.c.) (Fig.8), while gp. (5) noted disappeared in the sperm inside semineferous tubules. No distinctive pathological changes showed in gp.2 at 2nd (d p.c.), whereas, slightly degenerative changes showed in liver, spleen and kidneys of the same groups at 9th day post-cessation of treatment.

Histopathological examination revealed many pathological changes especially in liver and kidney (as the liver is the main organ of detoxication, while kidney is the main organ of excretion) which reflects the adverse effects of enrofloxacin and /or furosemide in treated rats. This may be attributable to interactions that occur within the body which

might be of pharmacokinetic or pharmacodynamic type. Furosemide was known to alter kinetics of some new fluoroquinolones decreasing the total and renal excretion of lomefloxacin in man ***(Sudoh et al., 1994)*** and difloxacin in goat ***(Fahim, 2005)*** accordingly furosemide may prolong duration of action of enrofloxacin, besides, quinolones were found able to induce singlet oxygen and superoxide anion that able to induce cellular DNA damage ***(Abd-Allah et al., 2000b)*** and so degenerative changes and necrosis . The precence of numerous lymphocytes in hepatic and renal parenchymae comes in agreement with, ***(Amer and EL-Shaieb, 1998)*** who stated that enrofloxacin administration to rabbits displayed aggregation of leucocytes mainly lymphocytes and macrophages replaced the necrotic hepatocytes, and ***(Anon, 2006)*** who stated Nephropathy is reported most commonly with ciprofloxacin (most common metabolite of enrofloxacin) This fluoroquinolone has been implicated in several cases of interstitial nephritis and it is unlikely that other nephropathologic changes will occur with preexisting decreased renal function (diuretic effect of furosemide).

The obtained pathological lesions of examined heart and spleen confirmed with ***(Amer and EL-Shaieb, 1998)*** who recorded depletion of lymphocytes from the white pulp in spleen, and extravasated blood among cardiac muscles in enrofloxacin treated rabbits.

Degenerative and necrotic changes among the semineferous tubules beside disappearance in the sperm inside semineferous tubules in all groups may be attributed to cellular DNA damage as discussed by ***(Abd-Allah et al., 2000b).*** these findings confirmed by ***(Abd-Allah et al., 2000a; Abd-Allah et al., 2000b; Demir et al., 2006*** and ***Aral et al., 2008)*** who stated degeneration of seminiferous tubules, incomplete

spermatogenesis and severe decrease in the concentration of sperms in seminiferous tubules up to necrobiotic changes in spermatogonial cells in rats treated with different fluoruquinolones.

Finally, pathological changes in livers and kidneys of furosemide treated rats were attributed to chemically reactive cytotoxic metabolite (7- ketocarboxylic acid) ***Butler et al., (2006) and Daniel et al., (2007).***

Table (2): Hemogram and blood indices of rats treated with enrofloxacin (10 mg kg^{-1}) and / or fruosemide (20 mg kg^{-1}) at the 2nd day post treatment. (X ± S.E.) (n=5).

Groups / parameters	gp : 1	gp : 2	gp : 3	gp : 4	gp : 5	gp : 6
WBCs (10^3/µl)	7.25 ± 0.140^a	7.32 ± 0.135^a	7.22 ± 0.124^a	7.13 ± 0.74^a	7.28 ± 0.70^a	7.17 ± 0.612^a
RBCs (10^6//µl)	6.8 ± 0.250^a	6.45 ± 0.005^b	6.21 ± 0.154^{bc}	5.21 ± 0.154^d	5.46 ± 0.271^d	5.40 ± 0.201^d
Hb (g dl)	13.67 ± 0.076^a	10.85 ± 0.157^b	10.54 ± 0.094^b	10.1 ± 0.045^c	10.07 ±0.30^c	10.08 ± 0.063^c
PCV (%)	38.89 ± 1.65^a	33.05 ± 0.251^{bc}	33.12 ± 2.21^b	28.68 ± 0.843^c	31.22 ± 0.725^{cd}	28.75 ± 1.85^c
MCV (μm^3)	57.15 ± 0.224^a	51.55 ± 0.201^f	52.02 ± 0.654^{bc}	55.2 ± 1.57^b	53.51 ± 0.832^{de}	53.91 ± 1.07^{cd}
MCH (pg)	20.10 ± 0.636^a	16.83 ± 0.255^c	16.66 ± 0.188^c	18.8 ± 0.080^b	18.53 ±0.503^b	18.65 ± 0.603^b
MCHC (%)	35.36 ± 1.31^a	32.44 ± 0.496^a	33.55 ± 1.82^a	35.35 ± 1.19^a	32.13 ± 0.241^a	32.23 ± 0.422^a

Means in the same rows bearing different letters superscripts differ significantly ($p<0.05$).

Table (3): Hemogram and blood indices of rats treated with enrofloxacin (10 mg kg^{-1}) and / or fruosemide (20 mg kg^{-1}) at the 9th day post treatment. (X ± S.E.) (n=5)

groups / parameters	gp : 1	gp : 2	gp : 3	gp : 4	gp : 5	gp: 6
WBCs (10^3 µl)	7.15 ± 0.21^a	7.24 ± 0.075^a	7.16 ± 0.179^a	7.06 ± 0.269^a	7.14 ± 0.194^a	7.26 ± 0.10^a
RBCs (10^6 µl)	7.11 ± 0.189^a	6.40 ± 0.069^b	6.28 ± 0.011^b	5.80 ± 0.022^{de}	5.82 ± 0.022^d	5.70 ± 0.05^{ef}
Hb (g dl)	13.98 ± 0.201^a	11.75 ± 0.186^b	11.23 ± 0.022^c	11.14 ± 0.045^{cd}	10.12 ±0.078^{ef}	10.26 ± 0.107^e
PCV (%)	37.89 ± 1.46^a	33.36 ± 0.392^b	31.79 ± 0.264^c	30.20 ± 0.173^{de}	30.23 ± 0.056^d	29.45 ± 0.201^{def}
MCV (μm^3)	52.71 ± 0.98^a	52.20 ± 0.084^{ab}	50.70 ± 0.313^c	52.07 ± 0.099^a	51.35 ± 0.157^{bc}	48.80 ± 1.71^e
MCH (pg)	19.75 ± 0.40^a	18.39 ± 0.487^c	17.90 ± 0.006^d	19.21 ± 0.003^b	17.39 ±0.070^e	17.99 ± 0.047^d
MCHC (%)	37.53 ± 1.03^a	34.65 ± 1.19^b	35.33 ± 0.221^b	36.91 ± 0.224^a	33.48 ± 0.198^c	34.84 ± 0.128^b

Means in the same rows bearing different letters superscripts differ significantly ($p<0.05$).

Table (4): Biochemical changes in serum of rats treated with enrofloxacin (10 mg kg^{-1}) and / or fruosemide (20 mg kg^{-1}) at the 2nd day post treatment. (X ± S.E.) (n=5)

group / parameters	gp : 1	gp : 2	gp : 3	gp : 4	gp : 5	gp : 6
ALT (iu/l)	23.4 ± 0.75^{d}	64.0 ± 1.79^{b}	64.4 ± 2.62^{b}	109.6 ± 1.63^{a}	109.8 ± 1.32^{a}	48.2 ± 2.27^{c}
AST (iu/l)	37.8 ± 0.74^{e}	159.2 ± 5.97^{c}	161.0 ± 8.05^{c}	233.0 ± 5.39^{b}	248.6 ± 2.11^{a}	74.8 ± 1.74^{d}
Total protein (g/l)	7.15 ± 0.15^{a}	7.10 ± 0.09^{a}	7.03 ± 0.224^{a}	7.01 ± 0.06^{a}	6.36 ± 0.09^{b}	6.99 ± 0.03^{a}
Albumin (g/dl)	4.47 ± 0.124^{a}	4.41 ± 0.051^{a}	4.40 ± 0.043^{a}	4.37 ± 0.041^{a}	4.06 ± 0.05^{b}	4.44 ± 0.048^{a}
Globulin (g/dl)	2.68 ± 0.064^{a}	2.69 ± 0.130^{a}	2.63 ± 0.260^{a}	2.64 ± 0.064^{a}	2.30 ± 0.088^{a}	2.55 ± 0.071^{a}
Glucose (mg/dl)	96.40 ± 2.41^{e}	95.60 ± 1.69^{e}	107.00 ± 2.24^{d}	115.00 ± 2.35^{c}	148.00 ± 2.37^{b}	152.00 ± 2.24^{a}
Creatinine (mg/dl)	0.68 ± 0.041^{f}	1.15 ± 0.10^{e}	2.5 ± 0.031^{c}	2.79 ± 0.027^{b}	4.14 ± 0.20^{a}	1.54 ± 0.084^{d}
Uric acid (mg/dl)	5.88 ± 0.133^{e}	6.86 ± 0.16^{d}	7.25 ± 0.618^{c}	7.91 ± 0.261^{b}	8.47 ± 0.082^{a}	7.20 ± 0.35^{cd}

Means in the same rows bearing different letters superscripts differ significantly ($p<0.05$).

Table (5): Biochemical changes in serum of rats treated with enrofloxacin (10 mg kg^{-1}) and / or fruosemide (20 mg kg^{-1}) at the 9th day post cessation of treatment. (X ± S.E.) (n=5)

groups / Parameters	gp : 1	gp : 2	gp : 3	gp: 4	gp : 5	gp : 6
ALT (iu/l)	24.80 ± 0.710^{f}	47.00 ± 1.23^{d}	58 ± 1.38^{c}	84.20 ± 2.20^{b}	108.00 ± 2.55^{a}	33.40 ± 1.20^{e}
AST (iu/l)	37.20 ± 0.860^{f}	49.60 ± 3.70^{d}	76.20 ± 1.74^{c}	80.6 ± 4.53^{b}	117.20 ± 1.39^{a}	41.40 ± 1.98^{e}
Total protein (g/l)	7.17 ± 0.131^{a}	7.21 ± 0.147^{a}	7.11 ± 0.492^{a}	7.13 ± 0.067^{a}	7.04 ± 0.291^{a}	7.15 ± 0.117^{a}
Albumin (g/dl)	4.37 ± 0.062^{a}	4.42 ± 0.102^{a}	4.40 ± 0.404^{a}	4.36 ± 0.022^{a}	4.12 ± 0.403^{a}	4.43 ± 0.135^{a}
Globulin (g/dl)	2.83 ± 0.132^{a}	2.79 ± 0.202^{a}	2.71 ± 0.636^{a}	2.77 ± 0.09^{a}	2.92 ± 0.112^{a}	2.72 ± 0.136^{a}
Glucose (mg/dl)	96.70 ± 0.527^{d}	97.00 ± 1.87^{d}	95.80 ± 2.59^{d}	104.00 ± 5.10^{c}	107.00 ± 4.47^{b}	113.00 ± 3.47^{a}
Creatinine (mg/dl)	0.674 ± 0.035^{f}	0.79 ± 0.016^{e}	1.29 ± 0.128^{c}	2.18 ± 0.113^{b}	3.64 ± 0.07^{a}	1.17 ± 0.146^{d}
Uric acid (mg/dl)	5.83 ± 0.111^{c}	5.55 ± 0.135^{c}	5.66 ± 0.401^{c}	6.48 ± 0.139^{b}	6.87 ± 0.262^{a}	5.70 ± 0.123^{c}

Means in the same rows bearing different letters superscripts differ significantly ($p<0.05$).

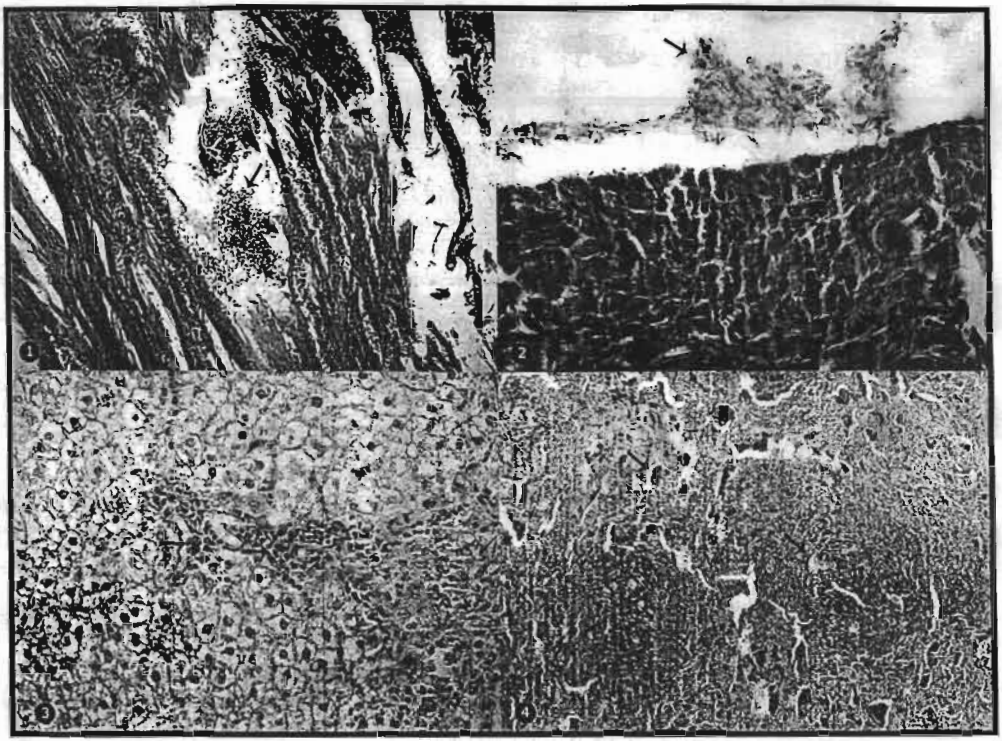

Fig. (1): Heart in gp. (5), 2 d p.c., showing severe hemorrhage with necrosis and destruction in the myocardium. (H&E., X 150)

Fig. (2): Heart in gp. (5), 9 d p.c., showing thickening in the pericardium with fibrous tissues proliferation. (H&E., X 300)

Fig. (3): Liver in gp. (6), 9 d p.c., showing telangectiasis in the blood sinusoids surrounded with aggregations of inflammatory cells, besides, vacuolar and hydropic degeneration and necrosis in some of the hepatic cells (H&E., X 300)

Fig. (4): Spleen in gp. (4), 9 d p.c. showing severe congestion in the blood sinusoids with depletion in the lymphocytes in white pulp. (H&E., X 150).

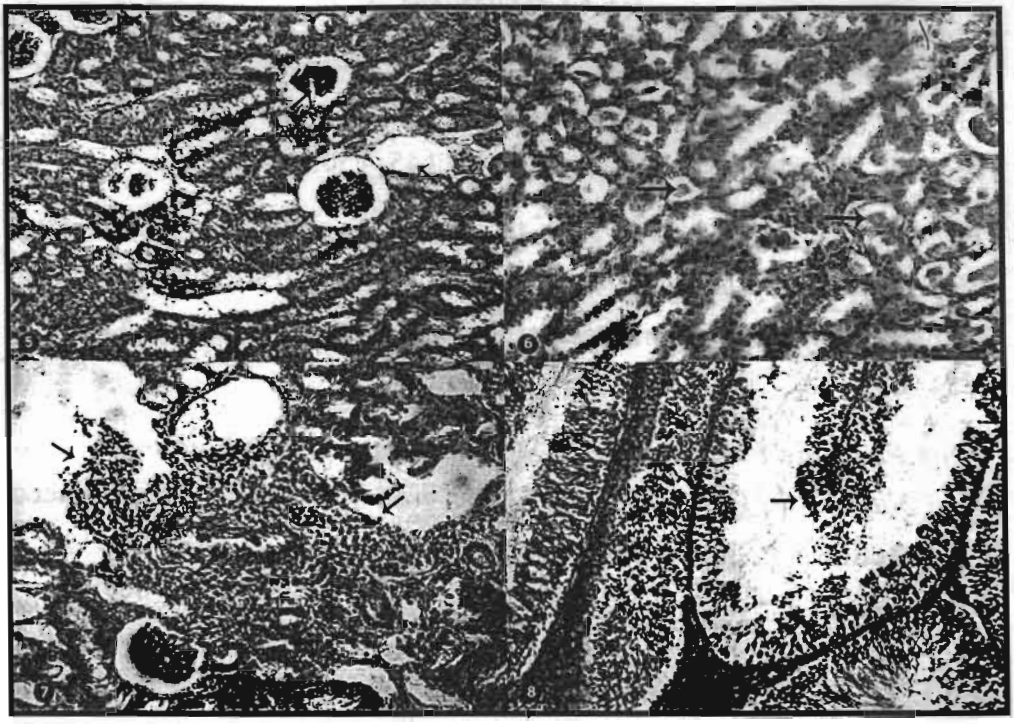

Fig. (5): Kidneys in gp. (4), 9 d p.c. showing edema in the bowman's space with contraction and disappeared in the glomeruli. (H&E., X 300)

Fig. (6): Kidneys in gp. (6), 9 d p.c. showing albumin casts inside the lumen of the collecting tubules. (H&E., X 300)

Fig. (7): Kidneys in gp. (5), 9 d p.c. showing thickening and edema in the wall of the blood vessels, surrounded with aggregations of the inflammatory cells. (H&E., X 300)

Fig. (8): Testis in gp. (3), 9 d p.c. showing destruction and edema in the semineferous tubules, beside degeneration and necrosis in the spermatogenesis. (H&E., X 600)

REFERENCES

- ***Abd-Allah, A.R.A.; Gannaham, B.B. and Hamada, A.M., (2000a):*** The impact of ofloxacin on rat testicular DNA: application of image analysis. Pharmacological Research 42, 145–150.
- ***Abd-Allah, A.R.A.; Aly, H.A.A.; Moustafa, A.M.A.; Abdel-Aziz, H.AA.and Hamada, F.A.M., (2000b):*** Adverse testicular effects of some quinolone members in rats. Pharmacological Research 41, 211–219.
- ***Abd El-Alim, F.A.; Amer, M.S.; Ramadan, O.E.; Mohamed. T.A. and Nagah, O. Edries (2000):*** Efficacy of ofloxacin against induced collibacillosis in broiler chickens. J. Vet. Med. Res., 2 (10) :113-123.
- ***Altreather, P. (1987):*** Data on chemistry and toxicology of Baytril. Vet. Med. Rev., 2:87-89.
- ***Amer, M.S. and El-Shaieb, A.F. (1998):*** Some adverse effects of enrofloxacin (Spectrama-vet)® in rabbit. 4th Vet. Med. Zag. Congress (26-28 august 1998) in Hurghada.
- ***Anon, (2006):*** The Fluoroquinolone Toxicity Research Foundation. The Quinolones and Fluoroquinolones. <http:/ /www. fqresearch. org/ m 23.htm>.
- ***Aral F.; Karacal F.and Fusun B. (2008):*** The effect of enrofloxacin on sperm quality in male mice. Research in Veterinary Science 84 (2008) 95–99.
- ***Bancroft, J.D.; Stevens, A. and Tumer, D.R. (1990):*** Theory and Practice of Histological Technique, 3rd Ed., Churchill, Livingstone, Edinburgh, London, Melbourne and New York.

- ***Briukhanov, V.M.; Zverev, F.I.; Lampatov, V.V and Zharikov, A.I (2007):*** Features of the pharmacodynamics and pharmacokinetics of furosemide upon long-term administration in rats. Eksp Klin Farmakol., 70(2):33-6.

- ***Butler, P.; Williams, D.; Jones, R.; Randle, L.; Payne, A.; Howard, M.; Gardner, I.; Blagg, J.; Dacie, J. V. and Lewis, S. M. (1974):*** Practical Haematology, Churchill Livingstone, Edinburgh, London, Melbourne and New York, pp.: 374 &438.

- ***Daniel, J.A.; Dominic, P.W.; Sophie, L.R. and Kevin Park B. (2007):*** Formation of cytotoxic protein reactive metabolites from furosemide: Biological consequences of drug metabolism. Toxicology, 240(3):157.

- ***Demir, A.; Turker, P.; Sirvancl, S.; Onol, F.F.; Flndlk, A.; Arbak, S. and Tarcan, T., (2006):*** The effects of acute epididimorchitis and ciprofloxacin treatment on testicular histo morphology and sperm parameters in rats. European Urology 5 (Suppl.), 214–241.

- ***Dimitriadis G.; Leighton, B.; Parry-Billings, M. and Newsholme, E.A. (1988):*** Effects of diuretic furosemide on the sensitivity of glycolysis and glycogen synthesis to insulin in the soleus muscle of the rat. Diabetologia, 31: 58-61.

- ***Dimitriadis, G.; Tegos, C.; Golfinopoulou, L.; Roboti, C. and Rapits, S. (1993):*** Furosemide induced hyperglycemia: The implication of glycolytic kinases. Hormone and Metabolic Research, 25: 257-259.

- ***Dimitriadis G.; Leighton, B.; Parry-Billings, M.; Tountas, C.; Rapits, S. and Newsholme, E.A. (1998):*** Furosemide decrease the sensitivity of glucose transport to insulin in skeletal muscle in vitro. European Journal of Endocinology, 139:118-122.

- ***Doxy, D.L. (1971):*** Vet. Clinical Pathology, 1st Ed., London, W.B. Saunders Company, pp.:556.

- ***Elen, M.E. (1990):*** Pharmacological studies on ciprofloxacin in chickens. Thesis presented to Fac., Vet., Med., Zag., Univ., for degree of Ph D (pharmacology).

- ***El-Sheikh, H.A.; Taha, A.A.W.; Khalafallah, A.I. and Osman, I.A.M. (2000):*** Disposition kinetic of enrofloxacin (Baytril 5%) in sheep and goat following intravenous and intramuscular injection using a microbiological assay. Research in Veterinary Science, 73:1125-129.

- ***Fahim, A.S. (2005):*** Pharmacokinetic studies on one of fluoroquinolones (difloxacin) in goats. Thesis presented to Fac., Vet., Med., Qena, South Valley Univ. for the degree of M.V.Sc. (pharmacology).

- ***Gassbarol, L.; Bedinelli, R. and Tomassin, G. (1972):*** Colorimetric determination of total proteins and albumin. Clin. Chem. Acta, 36:255.

- ***Gellert, Z.M. (1981):*** DNA topoisomerases. Annu. Rev. Biochem., 50:879-910.

- ***Halkin, H. (1988):*** Rev. Infec. Dis., 10:258-261.

- ***Helal, A.D.A.; El-Essaway, M.H.S.; Mousa, S.M. and Metwally, H.A. (1995):*** Effect of new antimicrobial drug enrofloxacin on histology and biochemical parameters of native broiler chickens. Zagazig Vet. J., 23(3):55-61.

- ***Henry, R.J.; Todd, S. and Davidsoh, N. (1974):*** Clinical Diagnosis And Measurement & Laboratory Methods, 16th Ed., W.B. Saunders Co. Philadelphia PA.,pp.:260.

- ***Hillel, H. (1988):*** Adverse effects of fluoroquinolones. Rev. Infec. Dis., 10 (Suppl. I):258-261.

- ***Hori, R.; Shimakura, M.; Aramata, Y.; Kizawa, I.; Takahata, M. and Minami, S. (2000):*** Nephrotoxicity of piperacillin combined with furosemide in rats. Jpn. J Antibiot., 53(8): 582-591.

- ***Ibrahim, F. M. K. (1995):*** Effect of enrofloxacin on the immune response of chickens under vaccination. Thesis presented to Fac. of Vet. Med. Zag. Univ. for the degree of M.V.Sc. (pharmacology).

- ***Kaneko, J.J.; Harvey, J.W. and Michael, L.B. (1997):*** Biochemistry of Domestic Animals, 5th Ed., Academic Press.

- ***Khodary, R.M. AND El-Sayed, E.M. (1997):*** Treatment of duckling salmonellosis by enrofloxacin. Assuit Vet. Med. J., 36(72):262-268.

- ***King, R.G. and Wooton, N.P. (1982):*** Microanalysis of Medical Biochemistry, 6th Ed., Churchill, Livingstone, London.

- ***Kirkendall, W.M. and Stein, J.H. (1968):*** Clinical pharmacology of furosemide and ethacrynic acid. American J. Cardiology, 22:162-167.

- ***Kobayashi, H. (1985):*** Summary of clinical studies on ciprofloxacin efficacy and adverse reactions. Proc. Of the 14th International Congress of Chemotherapy, Kyoto, Japan.

- ***Martinez, M.; McDemott, P. and Walker, R.(2006):*** Pharmacology of fluoroquinolones: A perspective for the use in domestic animals. The Veterinary Journal, 172:10-28.

- ***Ramadan, A.(1996):*** Pharmacokinetic aspects, egg distribution and residues of enrofloxacin in layer chickens. Bull. Fac. Pharm. Cairo Univ., 34(1):49-53.

- ***Rasha, A.N.(2008):*** Effects of some antibacterials in comparison with probiotic (Gallipro)® on broiler performance. Thesis presented to Fac. of Vet. Med. Suez Canal Univ. for the degree of Ph D (pharmacology).

- ***Reitman, S. and Frankel, S. (1957):*** Colorimetric determination of glutamic oxalacetic and glutamic pyruvic transaminases. Am. J. Clin. Path., 28:56.

- ***San Martin-Nunez, B.V.; Ordonez-Escudero, D. and Alunda, J.M.(1988):*** Preventive treatment of rabbit coccidiosis with α-difluoromethylorn: thine. Vet. Parasitol.,30:1-10.

- ***Sanofi-Avents, Canada Inc., (2007):*** Lasix oral solution (furosemide oral solution). 2150 st., Elzear Blvd. West Laval, Quebec H7L4A8. 1-26.

- ***Scheer, M. (1987):*** Studies on antimicrobial activities of Baytril. Veterinary Medical Revies, 2:331-348.

- ***Smith, D. and Park, B. (2006):*** Drug Metabolism Rev., 38 : 1-187.

- ***Snedecor, G.W. and Cochran, W.G. (1982):*** Statistical Methods, 7th Ed., Iowa state, USA.

- ***Steal, R.G.D. and Torrie, J.H.(1980):*** principle and procedures of statistics. A Biochemical Approach 2nd Ed., McGavous Hill Booh Company, New York, USA.

- ***Sudoh, T.; Fujimural, A.; Shigal, T.; Sasakil, M.; Haradal, K.; Tateishil, T.; Ohashil, K. and Ebiharal, A. (1994):*** Renal clearance of lomefloxacin is decreased by furosemide. European J. Clinical Pharmacol., 46(3):267-269.

- ***Trinder, P. (1969):*** Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. J Clin Pathol.. 22(2):158-61.

- ***Uyanik, F.; Liman, B.C. and Liman, N. (2000):*** The effects of danofloxacin on some biochemical parameters and liver in broilers. Vet. Bull., 70(3):358.

- ***Vancutsem, P.M.; Babish, J.G. and Schwark, W.S. (1990):*** The fluoroqunolone antimicrobials: structure, antimicrobial activity, pharmacokinetics, clinical use in domestic animals and toxicity. Cornell Veterinarian, 80:173-186.

- ***Walker, R.D.; Stein, G.E.; Hauptman, J.G. and McDonald, K.H. (1992):*** Pharmacokinetic evaluation of enrofloxacin administered orally to healthy dogs. American Journal of Veterinary Research. 53: 2315-2319.

- ***Young,D.;Pestaner. L. and Giberman, V.(1975):*** Clin. Chem.. 21:10.

بعض الآثار الجانبية للتداخل الدوائي بين الفيوروزاميد و الإنروفلوكساسين في الفئران البيضاء

أشرف الغنيمي[1] ، حازم شاهين[1] ، مشيرة محى[2] ، وجيه الشيخ[3] ، رمضان طه[4]

[1] قسم الفارماكولوجيا- كلية الطب البيطري – جامعة جنوب الوادي بقنا

[2] قسم الباثولوجيا – كلية الطب البيطري – جامعة جنوب الوادي بقنا

[3] معهد بحوث صحة الحيوان الفرعي بطنطا

[4] قسم الباثولوجيا الإكلينيكية – كلية الطب البيطري – جامعة قناة السويس

يعد الاستخدام المتزامن للمضادات الحيوية و مدرات البول شائعا" في حالات العدوى الحادة الشديدة عندما تكون هناك حاجة لزيادة إدرار البول أو في الحالات التي تعاني فيها الحيوان من وجود إرتشاح مائي مصحوبا بالعدوى البكتيرية. أجريت هذه الدراسة على عدد (6) مجموعات متساوية من الفئران قوام كلا منها (10) فئران، المجموعة الأولى: تركت بدون علاجات و اعتبرت كمجموعة ضابطة، المجموعة الثانية: حقنت عضليا بعقار الإنروفلوكساسين (10 ملجم / كجم من وزن الجسم الحي) لمدة 5 أيام متتالية، المجموعة الثالثة: حقنت عضليا بعقاري الإنروفلوكساسين (10 ملجم / كجم من وزن الجسم الحي) لمدة 5 أيام متتالية و الفيوروزاميد (20 ملجم / كجم من وزن الجسم الحي) وذلك في اليوم الأول من حقن الإنروفلوكساسين، المجموعة الرابعة: حقنت عضليا بعقاري الإنروفلوكساسين (10 ملجم / كجم من وزن الجسم الحي) لمدة 5 أيام متتالية و الفيوروزاميد (20 ملجم / كجم من وزن الجسم الحي) وذلك في اليوم الأول و الثالث من حقن الإنروفلوكساسين.

المجموعة الخامسة: حقنت عضليا بعقاري الإنروفلوكساسين (10 ملجم / كجم من وزن الجسم الحي) لمدة 5 أيام متتالية و الفيوروزاميد (20 ملجم / كجم من وزن الجسم الحي) وذلك في اليوم الأول و الثالث و الخامس من حقن الإنروفلوكساسين، لمجموعة السادسة: حقنت عضليا بعقار الفيوروزاميد (20 ملجم / كجم من وزن الجسم الحي) و ذلك يوم بعد يوم في خلال خمسة أيام متتالية (اليوم الأول، الثالث و الخامس). تم حقن الفيوروزاميد قبل ميعاد حقن الإنروفلوكساسين

بساعة. تم ذبح عدد (5) فئران من كل مجموعة و ذلك في اليوم الثاني و اليوم التاسع بعد انتهاء فترة الحقن مع تجميع عدد (2) عينة دم من كل فأر، واحدة في وجود مانع للتجلط و ذلك لدراسة بعض التغيرات في الدم أما الأخرى بدون مواد مانعة للتجلط و ذلك للحصول على مصل الدم لقياس بعض المكونات البيوكيميائية. تم أخذ عينات من كل من الكلى، الكبد، القلب، الطحال و الخصيتين من كل فأر و ذلك للفحص الهستوباثولوجي.

و قد أظهرت النتائج المتحصل عليها نتيجة الفحص الدموي حدوث نقصا معنويا في كرات الدم الحمراء، مستوى الهيموجلوبين، حجم الكريات المرصوصة، متوسط حجم الكريات متوسط هيموجلوبين الخلية و كذلك متوسط تركيز هيموجلوبين الخلية و ذلك في كل المجموعات المعالجة. و قد كانت هذه التأثيرات أكثر شدة في المجموعة المحقونة بكل من العقارين و بالأخص في المجموعة الرابعة و الخامسة. و قد أوضحت النتائج المتحصل عليها نتيجة الفحص البيوكيميائي حدوث زيادة معنوية في مستوى كل من إنزيمات الألانين و الأسبرتيت ترانسفيريز، الكرياتينين و حمض البوليك في كل المجموعات المعالجة و قد كانت هذه التأثيرات بكل من العقارين و بالأخص المجموعات الثالثة، الرابعة و الخامسة. كما أظهرت النتائج أيضا حدوث زيادة معنوية في مستوى جلوكوز الدم و ذلك في المجموعة المعالجة بالفيوروزاميد (الرابعة) و كذلك المجموعات المعالجة بكل من الفيوروزاميد و الإنروفلوكساسين (الثالثة و الرابعة و الخامسة). كما أظهرت النتائج حدوث نقصا معنويا في مستوى البروتينات الكلية و الزلال في دم فئران المجموعة الخامسة. و قد أشار الفحص الباثولوجي إلى وجود نزف دموي مختلف الدرجات مع تنكرز في عضلة القلب ، زيادة سمك غشاء التامور نتيجة زيادة الأغشية الفبرينية. أتساع الجيوب الدموية و أحاطتها بتجمعات من الخلايا الالتهابية مع و جود تغيرات تحطيمية و تنكرزية في بعض خلايا الكبد.

احتقان شديد في الجيوب الدموية مع استنزاف الخلايا الليمفاوية بالقالب الأبيض بالطحال. إرتشاح مائي في محفظة باومان مع اختفاء بعض الضفيرات الدموية مع وجود أجسام زلالية بتجويف الأنابيب المجمعة في الكلى..إرتشاح مائي مع تدمير بعض الأنابيب المنوية و تغيرات تحطيمية بالخلايا المكونة للحيوانات المنوية.