Some Pharmacological And Toxicological Studies On Flubendazole In Broilers

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ABSTRACT

Flubendazole is one of benzimidazoles compounds mainly used as broad spectrum anthelmintic in Veterinary Medicine. This study aimed to investigate the adverse effects induced by flubendazole over dose in correlation to its residues in broiler chickens. Fourty eight mature broiler chickens (sasso), three months old, weighing about 1250gm, were classified into 4 equal groups, the first group served as control, while the second group received the therapeutic dose of flubendazole for broilers (30 gm/ton of ration).The third group received double therapeutic dose (60 gm/ton of ration). The fourth group received triple therapeutic dose (90 gm/ton of ration).Six birds from each group were sacrificed 24 hours post treatment while the rest of birds were sacrificed one week post treatment to clarify the withdrawal time of drugs. Blood samples were collected for biochemical and haematological studies. Specimens were obtained for pathological and residual detection of the drug. No adverse effects could be detected on using the therapeutic dose on tissue histology, haematology, clinical chemistry and tissue residues of flubendazole.Broilers that received double and triple therapeutic doses of flubendazole were dull with low performance, off food ,hematologically showed marked anemia, with significant diminished values of erythrocytes and PCV especially in group received triple therapeutic dose ,leucopenia was also marked in these groups. Although significant elevation of liver enzymes (AST, ALT and ALP) activities and the levels of total bilirubin, there was marked hypoproteinamia and hypoalbuminemia in groups received double and triple therapeutic doses on 24 hours and one week post cessation of drug administration. On the other hand degenerative and necrotic changes were observed in hepatic and renal tissues. Spleens showed marked lymphocytic depletion of the lymphoid follicle, intestine showed obvious enteritis with heavy infiltration of inflammatory cells, beside vacuolar degeneration of skeletal muscles. Residual detection of flubendazole and its metabolites revealed that liver, kidneys and muscles has the maximum residual level which increased along with the doses. Finally it can be concluded that the marked adverse effects may be due to drug toxicity which leads to depression of haemobiotic system, renal and hepatic damage, so on using flubendazole as anthelimintic, withdrawal time must be taken in concern for consumer and broiler safety.

INTRODUCTION

Veterinary drugs are widely used for treatment and prevention of diseases in livestock. Inadequate use of these drugs can leave residues in edible tissues, which can lead to human health problems *(1)*.

Flubendazole ([5-(4-fluorobenzoyl)-1H-benzimidazole-2-y1]-carbamic acid methyl ester) belongs to the group of benzimidazole carbamates.It is mainly used as a broad-spectrum anthelmintic in Veterinary Medicine. It has been widely available in many countries, even in human medicine *(2)*. This compound belonging to a group of chemical compounds which are effective in controlling intestinal parasites like round worms, tape worms and pin worms, etc. These compounds are not antibiotics or antifungal and in fact may escalate these problems as they kill off other infections. It is administered orally to pigs, chickens and game birds *(3)*.

Flubendazole is poorly absorbed by GIT and metabolized in a qualitatively similar way in all species studied. More than 50% of the ingested drug is eliminated unchanged in the faeces. The absorbed drug is rapidly metabolized, so that levels of parent drug in

the blood and urine are extremely low. The main site of metabolism is the liver, and the major metabolic pathways are carbamate hydrolysis and ketone reduction. To some extent, methylation has also been found as a relatively minor pathway. ***(4).***

It seems that flubendazole undergoes enterohepatic circulation. The biotransformation of flubendazole was extensive and follows similar metabolic pathways in pigs, chickens and turkeys ***(5).*** Keratoreduction of flubendazole to R038758 or M8 was the major metabolic pathway in chickens and turkeys. Carbamate hydrolysis to R034575 or M7 was the major metabolic pathway in pigs, both metabolites were later converted to another compound known as R045198 or M6. Conjugation of M8 and M6 also occurred, it was noted that the metabolites retained the benzimidazole structure and were likely to have toxicological properties similar to those of flubendazole ***(6).***

The aim of this work was to study and characterize the adverse effects induced by flubendazole in broilers. This investigation was also focused on its residues in different tissues of broilers and the possible correlation between the dose and tissue residues to ensure food safety for consumer.

MATERIALS AND METHODS

1-Birds

Fourty eight mature male broiler chickens (sasso), three months old, weighing about 1250gm used in this study, they were obtained from broiler farm in Sharkia Province.

Birds were kept in cages (6 birds per cage) and received the normal broiler feed and water *ad labium*.

Birds were kept for one week for accommodation to lab conditions before beginning of the experiment.

2-Drug

Flubendazole (Fluwomex)® for oral administration, Bremer Pharma GMBH 27540 Bremerhaven, Germany, Purity 99%,its dose for broilers is 30 gm flubendazole (60 gm Fluwomex)/ ton of feed for 7 days.

3-Grouping and experimental design

Birds were classified to 4 equal groups each of 12, the first group served as control non treated while the second group received the therapeutic dose of flubendazol for broilers (30 gm/ton of ration for 7 fays) following the instruction of Manufacture Company. The third group received double therapeutic dose (equivalent to 60 gm/ton of ration for 7 days).The fourth group received triple therapeutic dose of flubendazole (90 gm/ton of ration for 7 days).

Six birds from each group were sacrificed 24 hours post treatment while the rest of birds sacrificed one week post treatment to clarify the withdrawal time of drug. Blood samples were collected from all birds, blood were taken on EDTA – coated tubes for haematological study, serum separation to another samples for biochemical determination of liver function and kidney function tests.

4-Haematological analysis

Erthrocytic count (RBCs) was done using Neubauer hemocytometer and growers diluting fluid ***(7).*** Packed cell volume (PCV) was estimated by the microhematocrit centrifuge ***(8).*** Hemoglobin (HB) estimation was performed using the cyanomethemoglobin colorimetric method ***(9).*** Total leucocytic count (TLC) was performed using improved Neubauer hemocytometer and Turkeys diluting fluid. Differential leucocytic count by preparation of blood film, stained with Giemsa stain and the differential count was done and then the absolute counts were calculated for lymphocytes and neutrophils ***(8).***

5-Biochemical analysis

Serum aniline aminotransferase (ALT), aspartate aminotransferase (AST) ***(10)*** and alkaline phosphatasae (ALP) were determined ***(11).***

Serum total proteins ***(12),*** albumin ***(13)*** were determined, serum globulins were calculated by subtraction of albumin level from total proteins.

Serum total bilirubin ***(14),***While, uric acid

level was determined by enzymatic colorimetric test (uricase-PAP) using diagnostic kits (Diamond, Diagnostics) according to *(15).*

6-Pathological studies

Post mortem (PM) examination was carried out carefully on all birds and any abnormality was recorded.

Specimens from liver, kidney, spleen, testis, intestine and skeletal muscles were obtained from sacrificed birds of all experimental groups and fixed in neutral-buffered formalin. Then specimens were routinely processed and sectioned at 4-5um thickness. The obtained sections were stained with H&E *(16).*

7-Tissue residues

Extraction from tissues was done according to **Heitzman** *(17).* After evaporation, the chloroform residue was dissolved in 125 ul water giving a total volume of 250ul. Volume injected into HPLC system was 50 ul.

The chromatographic analysis of flubendazole and its internal standard was done according to **El-Kholy and Kemppainen,** *(18).* The column was Luna mm × 4.6 mm and the mobile phase consisted of one liter 2% acetic acid in water: methanol (50:50,v/v) and one bottle of PICB-7 low UV reagent. The pH of the mobile phase was adjusted to 7.31 with concentrated ammonium hydroxide solution. Flow rate was 1ml/ min. The UV detection was at wave length of 225nm.

8-Statistical analysis

The results were analyzed according to **Snedecor and Cochran** *(19).*

RESULTS

The administration of flubendazole to broiler ration with therapeutic dose revealed that, no adverse effects could be detected on tissue histology, hematology, clinical chemistry and tissue residues of flubendazole. The latter parameter was nearly the same like the recommended Maximum residual levels (MRls). While, broiler groups that were treated with double and triple therapeutic doses showed variable adverse effects on the last mentioned parameters. These alterations were dose and time related.

Broilers received three fold the therapeutic dose were dull with low performance, and marked off food. At necropsy, parenchymatous organs of broilers that received both double and triple therapeutic doses showed liver, kidney and spleen enlargement, pale in color, and sometimes there were areas of congestion. The intestinal mucosa was congested. The lesions were more pronounced in the group treated with triple dose of flubendazole.

Haematological results

RBCs count was significantly reduced in a dose-dependent manner and the highest degradation level was remarked with the group received the three fold dose (90gm) 24 hours post drug administration while it showed significant decrease only in three fold dose (2.8±0.6) one week post stoppage of drug administration (Table 1.).

The PCV value was significantly lowered in broilers received double and triple the doses. This decrement was marked in both groups sacrificed 24 hours and one week after stoppage of flubendazole administration (Table 1).

Total leucocytic count showed marked elevation which is dose- dependent, the highly significant response was marked in three fold groups (24 hours and one week post stoppage of drug administration).

Neutrophils and lymphocytes % were significantly decreased in double and three fold doses either after 24 hours or after one week from cessation of drug administration (Table 1).

Table 1. The effect of flubendazole on haematological parameters of broilers treated with therapeutic, double and 3 fold therapeutic doses for 7 days (Mean ± SE)(n=6).

Time / Group and treatment	Twenty four hours post treatment						one week post treatment					
	RBCs 10^6x cu mm)	PCV %	Hb (gm/L)	WBCs (10^3xcu mm)	Neutrophil %	Lymphocyte %	RBCs 10^6x cu mm)	PCV %	Hb (gm/L)	WBCs (10^3xcu mm)	Neutrophil %	Lymphocyte %
Control group(G1)	4.1 ± 0.4	37.9 ± 0.3	7.7 ± 0.2	28.4 ± 2.3	22.3 ± 0.7	16 ± 1.3	4.2 ± 0.5	38.2 ± 0.1	8.1 ± 0.2	27.1 ± 1.3	23.3 ± 0.9	15 ± 1.1
Therapeutic Dose(G2) (30gm/ton)	3.9 ± 0.33	32.5 ± ** 0.26	8.2 ± 0.45	29.6 ± 1.9	22.6 ± 1.1	14 ± 1.1	3.8 ± 0.8	36.0 ± 0.4	8.4 ± 0.3	24.5 ± 0.9	23.7 ± 2.2	13 ± 0.9
Double Dose(G3) (60gm/ton)	3.2 ± 0.29	34.0 ± * 0.27	7.4 ± .09	22.5 ± 2.1*	15.3 ± ** 0.8	12.2 ±** 0.6	3.9 ± 0.4	30.0 ±** 0.2	7.6 ± 0.5	23.7 ± 1.6	12.8 ± 0.6	12.4 ± * 0.9
3 fold Dose(G4) (90gm/ton)	2.6 ±** 0.04	23.0 ±** 0.2	7.5 ± 0.14	19.6 ± ** 2.2	12.0 ± ** 0.3	10.9 ±** 0.7	2.8 ±** 0.6	24 ±** 0.3	7.9 ± 0.2	20 ± 1.9	14.8 ± 1.1	9.7 ±** 0.7

* $P < 0.05$ (Significant). ** $P < 0.01$ (Highly significant).

Biochemical results

AST, ALT, Alkaline phosphatase (ALP) activities and total bilirubin (TB) concentration were significantly elevated in serum of broilers received double and triple therapeutic doses of flubendazole either after 24 hours or after one week from stoppage of drug administration (Table 2) .

Both total proteins and albumin levels were significantly lowered in double and triple doses groups after 24 hours and one week post cessation of the drug (Table 2).

Finally uric acid concentration showed highly significant elevation in both double and triple therapeutic doses after 24 hours and one week post cessation of drug administration (Table 2).

Residual results

Regarding Maximum residual levels (MRLs) of flubendazole and its metabolite 2-amino-1H-benzimidazole-5-yl. liver tissues had the highest concentrations of flubendazole and its metabolite which increased gradually by increasing the drug dose showing the highest level (884 ug/kg) in group received 3 fold the therapeutic dose after 24 hours from cessation of drug administration. After one week post stoppage of drug administration the residual level in liver is lowered and reached 551 ug/kg but it still highly significant elevated than the therapeutic residual level in liver (218ug/kg) (Table3).The concentration of flubendazole and its residue 2-amino-1H-benzimidazole-5-yl in both kidney and muscles of broilers after one week of stoppage of drug administration in both double therapeutic dose were 274, 413 ug/kg respectively and triple therapeutic doses were 301, 495ug/kg respectively, it still significantly higher than therapeutic residual levels (97, 173 ug/kg respectively) (Table 3.).

Table 2. The effect of flubendazole on biochemical parameters of broilers treated with therapeutic, double and 3 fold therapeutic dose for 7 days (Mean ± SE)(n=6)

Time / Group and treatment	Twenty four hours post treatment							One week post treatment						
	AST U/L	ALT U/L	ALP Kul/dl	Total Bilirubin mg/dl.	Total protein mg/dl	Albumin mg/dl	Uric acid mg/dl	AST U/L	ALT U/L	ALP Kul/dl	Total Bilirubin mg/dl.	Total protein mg/dl.	Albumin mg/dl	Uric acid mg/dl
Control group(G1)	21.3± 0.6	18.8 ± 0.2	9.8 ± 0.3	0.4 ± 0.01	2.8 ± 0.2	0.66 ± 0.03	5.4 ± 0.2	22.1± 0.9	19.3 ± 0.7	10.5 ± 0.04	0.4 ± 0.02	2.9 ± 0.4	0.7 ± 0.03	5.6 ± 0.4
Therapeutic Dose(G2) (30gm/ton)	22.4± 0.9	20.1 ± 0.4	10.2 ± 0.4	0.4 ± 0.02	2.78 ± 0.3	0.7 ± 0.02	5.5 ± 0.3	21.8± 0.3	19.8 ± 0.2	10.1 ± 0.6	0.4 ± 0.01	2.7 ± 0.6	0.6 ± 0.01	5.6 ± 0.6
Double Dose(G3) (60gm/ton)	29.6 ±** 1.6	27.4 ±** 2.3	16.2 ±** 1.4	0.7 ±** 0.03	1.9 ±** 0.1	0.4 ±** 0.01	7.9 ± 0.2	27.6± 1.1	25.8 ±** 0.3	14.4 ±** 0.8	0.6 ±** 0.03	2.1 ±* 0.2	0.5 ±** 0.02	7.5 ± 0.1
3 fold Dose(G4) (90gm/ton)	36.8 ±** 2.1	30.4 ±** 1.9	19.4 ±** 1.8	1.1 ±** 0.06	1.2 ±** 0.08	0.2 ±** 0.03	9.8 ± 0.7	36.1±* * 1.8	29.8 ±** 0.1	19.8 ±** 1.2	0.9 ±** 0.05	1.3 ±** 0.07	0.3 ±** 0.02	9.3 ± 0.6

* $P < 0.05$ (Significant). ** $P < 0.01$ (Highly significant).

Table 3. The concentration of flubendazole and its metabolite (2-amino-1H-benzimidazole-5-yl) in liver, kidney and muscle (µg/kg)24 hours and one week post treatment of broilers by therapeutic, Double and 3 fold therapeutic doses for one week. (Mean ± SE) (n=6).

Time / Group and treatment	24 hours post treatment			One week post treatment		
	Liver	Kidneys	Muscles	Liver	Kidneys	Muscles
Therapeutic Dose (30gm/ton)	473 ± 0.06	164 ± 0.07	303 ± 0.09	187 ± 0.06	97 ± 0.08	113 ± 0.06
Double dose (60gm/ton)	642** ± 0.006	311** ± 0.004	498** ± 0.009	412** ± 0.01	234** ± 0.007	383** ± 0.004
3 fold Dose (90gm/ton)	884** ± 0.009	389** ± 0.003	633** ± 0.007	551** ± 0.01	301** ± 0.005	495** ± 0.006

** $P < 0.01$ (Highly significant).

Histopathological results

Microscopical examination of tissue sections of all treated groups revealed mild pathological changes in chickens given the therapeutic dose of flubendazole. Only mild degenerative changes were observed in liver, kidney and spleen, but no observable changes could be detected in muscles of this group.

Marked pathological alterations were observed in those groups treated with double and triple therapeutic dose of flubendazole. The changes were dose and time related, include conspicuous degenerative and necrotic changes in hepatic and renal tissues. The former tissue revealed dilated sinusoids, dissociation of hepatocytes, granular and vacuolar degeneration **(Fig.1a).** Marked replacement of the necrotic cells with large number of mononuclear inflammatory cells in a focal manner **(Fig. 1b).** Also cytomegally was an obvious finding among the altered hepatocytes. Renal tissues of G3 and G4 showed clear swelling with granular and vacuolar appearance of the cytoplasm of the renal tubular epithelial lining accompanied with early little tubular regeneration. An obvious desquamation of those epithelial cells was observed **(Fig. 1c,d)** along with congestion of the renal blood vessels, focal interstitial round inflammatory cells infiltration and hypercellularity of the glomeruli **(Fig.1e).** Spleen of large number of birds showed marked lymphocytic depletion of the lymphoid follicle **(Fig.1f)** with the appearance of the underlining reticular mash as well as reduction in the white bulb area with decreased RBCs in the red bulb.

Conspicuously, the GIT was influenced. It revealed obvious enteritis characterized by heavy infiltration of the intestinal mucosa with large number of inflammatory cells **(Fig. 2a),** marked desquamation of the intestinal epithelial cells and accumulation of large amount of inflammatory exudates admixed with inflammatory cells along the intestinal lumen **(Fig.2b).** Marked depletion of the gut associated lymphoid aggregates **(Fig. 2c).**

Examination of skeletal muscle sections from different areas revealed an obvious vacuolar degeneration of the muscle fibers and mild hyalinization especially in G4 with evidence of early inflammatory infiltrates **(Fig. 2d).**

Testicular tissue of G4 chicks revealed degenerative and necrotic changes in the spermatogonial cells layers with a clear disorganization **(Fig. 2e,f).**

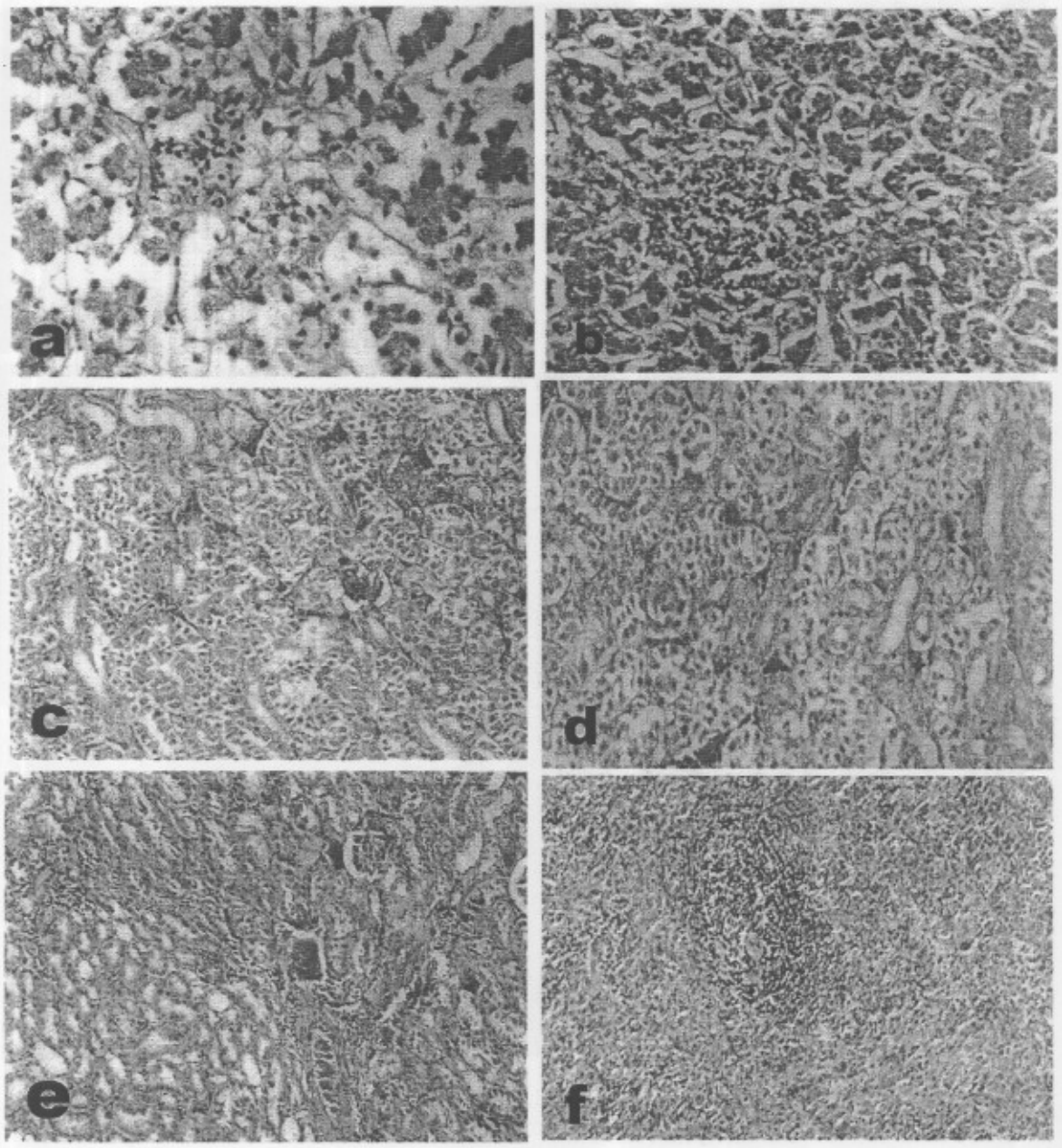

Fig 1. Photomicrograph of the **a-** liver of G3 chick showing; degeneration and necrosis of hepatocytes. **b-** liver of G3 chick showing; replacement of necrotic hepatocytes with focal mononuclear inflammatory cells. **c and d-** kidney of G4 chick showing degenerative and necrotic changes of the renal tubular epithelial cells with evident desquamation of most of them. **e-** kidney of G3 chick revealing focal interstitial nephritis. **f-** Spleen of G3 chick revealing early lymphocytic depletion of the lymphoid follicles. (H&E X200, 400) .

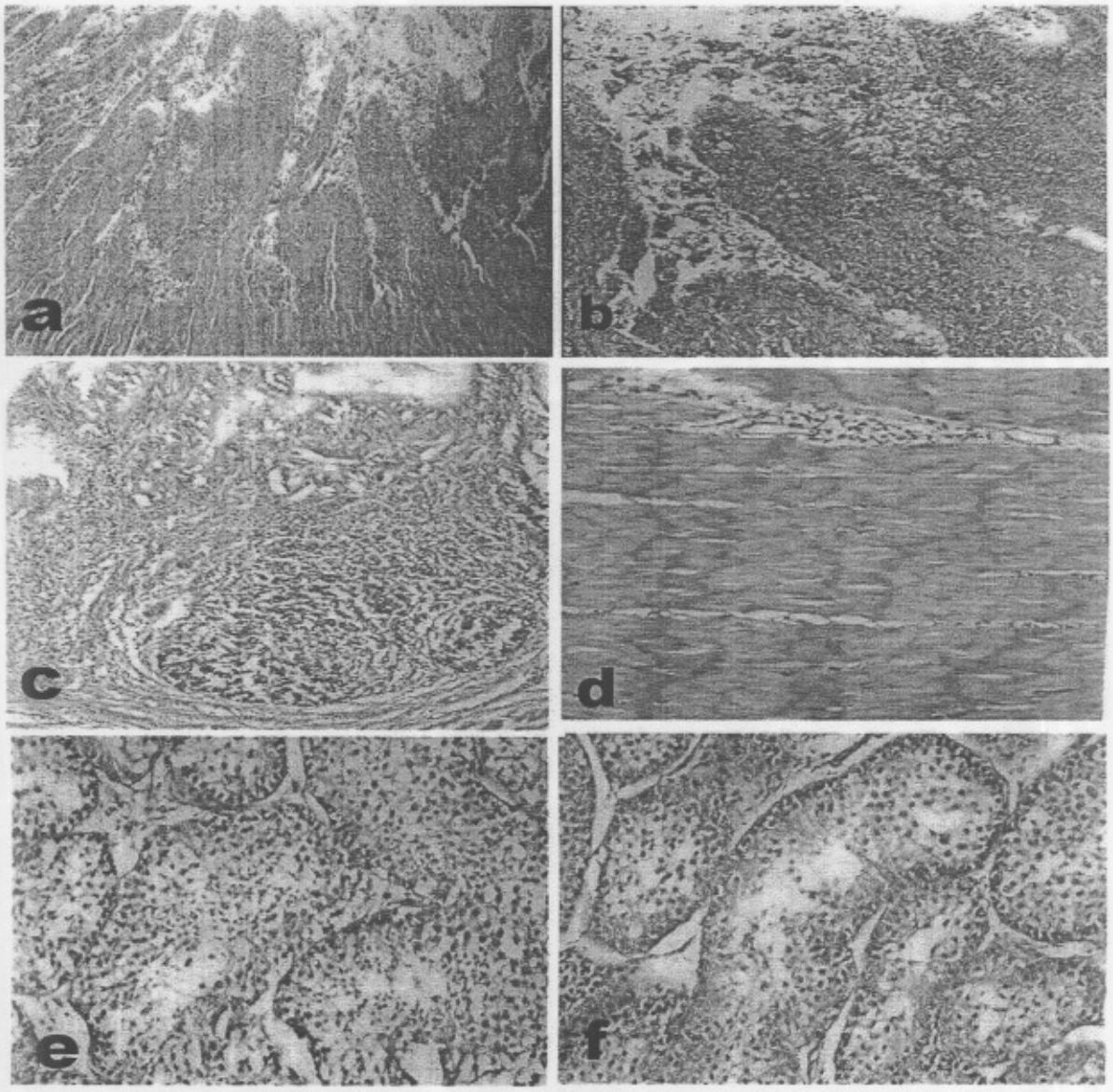

Fig 2. Photomicrograph of the **a- c:** Intestine of G4 chick reveling: **a-** Enteritis with desquamation of the epithelial lining. **b-** Accumulation of inflammatory exudates in the lumen of the intestine. **c-** Depletion of lymphocytes from the gut associated lymphoid follicles. **d-** skeletal muscles of G4 chick reveling mild degeneration of the muscle fibers with focal round cells infiltration. **e and f-** Testis of G4 chick showing necrosis of spermatogonial cells and disorganization of their layers with absence of mature spermatid and sperm. (H&E X200, 400).

DISCUSSION

Broilers received double and triple therapeutic doses of flubendazole were dull with low performance and off food compared with control and therapeutically treated broilers. On the blood picture there was marked anemia, with significant diminished values of erythrocytes and PCV especially in group received 3 fold doses which might be due to drug toxicity due to reduced erythropoietin hormone production from the damaged kidney tissues. These results were supported by the pathological findings in this study which represented by clear swelling with granular and vacuolar appearance of the cytoplasm of the renal tubular epithelial lining with obvious desquamation of these epithelial cells.

Leucopenia observed in this results manifested by neutropenia and lymphopenia especially in the highest dose group (group 4) after 24 hours and one week post cessation of drug might be attributed to depression of haemobiotic system caused by drug toxicity which was assured pathologicaly with marked lymphocytic depletion of the lymphoid follicle of spleen beside lymphoid aggregates and inflammatory infiltrates in gut of broilers.

On the other hand, liver enzymes (AST, ALT and alkaline phosphatase activities) and total bilirubin were significantly elevated with the highest significant increase in the fourth group (triple therapeutic dose) after 24 hours and one week post cessation of drug. On the other hand, the marked hypoproteinamia and hypoalbuminemia which might be due to renal and hepatic damage was confirmed by histopathological results as degenerative and necrotic changes in both hepatic and renal tissues beside higher residual levels of flubendazoles and its metabolite (2-amino-1H-benzimidazole-5-yl) in both hepatic and renal tissues *(20).*

Leemput,*(4)* reported that flubendazole exhibits enterohepatic circulation and this in agreement with obtained pathological and residual findings of flubendazole in hepatic tissues. Reduction of the ketone functional group and hydrolysis of the carbamate moiety are the main biotransformation pathways of flubendazole in pigs, chicken and turkeys. To some extent, methylation has also been found as a relatively minor pathway. In rats and dogs, the urinary metabolites are formed exclusively by ketone reduction, carbamate hydrolysis and glucuronide and sulfate conjugation *(21).*

Uric acid concentration was significantly elevated in double and triple therapeutic doses. This is a good marker for renal damage and is supported by pathological findings and by high residual levels in renal tissues. The higher residues of flubendazole and its metabolite (2-amino-1H-benzimidazole-5-yl,) were marked in liver then muscles and then the kidneys, particularly in groups received double and three fold therapeutic doses either after 24 hour or one week of cessation of drug administration. **Price** *(22)* reported that flubendazole, mebendazole, oxfendazole, oxibendazole and parbendazole were metabolized in the liver. Residues of the parent drugs and their metabolites may be found in the tissues for extended periods of time (> 20 days) although all current information indicates that no problems should arise if the recommended withdrawal periods are allowed.

We conclude that the dose and withdrawal time must be kept in mind following the instruction of Manufacture Company during using flubendazole as anthelemintic for keeping the health condition of poultry and consumers.

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الملخص العربى

بعض الدراسات الدوائية والسمية على عقار الفلوبندازول في الدجاج

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عقار الفلوبندازول هو واحد من مجموعة البنذيميدازول ويستخدم اساسا كمضاد للديدان واسع المدى في الطب البيطري. وتهدف هذه الدراسة إلى دراسة الآثار الضارة التي تحدثها الجرعات الزائدة من عقار الفلوبندازول ارتباطا ببقايا العقار فى الدجاج.فى هذه الدراسة تم استخدام ثمانية وأربعون دجاجة (ساسو) ، البالغ من العمر ثلاثة أشهر ، وتزن حوالى ١٢٥٠جرام ، تم تصنيفها إلى ٤ مجموعات كل مجموعة١٢ دجاجة ، المجموعة الأولى المجموعة الضابطة ، في حين أن المجموعة الثانية تم إعطائها الجرعة العلاجية لعقار الفلوبندازول (٣٠ جم / طن عليقة لمدة سبعة أيام) . المجموعة الثالثة أخذت ضعف الجرعة العلاجية (٦٠ جم / طن عليقة لمدة سبعة أيام). المجموعة الرابعة تلقت ثلاثة أضعاف الجرعة العلاجية من العقار (٩٠ جم / طن عليقة لمدة سبعة أيام). ستة طيور من كل مجموعة تم ذبحها بعد انتهاء العلاج ب ٢٤ ساعة بينما بقية الطيور تم ذبحها بعد أسبوع واحد من انتهاء العلاج لتوضيح فترة سحب الدواء. تم جمع عينات الدم لعمل التحاليل البيوكيمائية وكذلك صورة الدم للدجاج المعالج.تم اخذ عينات لإجراء الفحوص الهستوباثولوجية والكشف عن بقايا العقار.أظهرت النتائج أنه لا توجد آثار سلبية على المجموعة التى عولجت بالجرعات العلاجية على الأنسجة والدم(التحاليل البيوكيمائية وصورة الدم) وبقايا العقار فى الأنسجة. بينما المجموعات التى أخذت جرعة مضاعفة وجرعة ثلاثية من العقار لوحظ أن الطيور ظهر عليها الكسل مع انخفاض الأداء ، وفقدان الشهيه وصورة الدم أظهرت أن هناك نقص ملحوظا فى كرات الدم الحمراء وحجم الخلايا المضغوطة مع ظهور علامات فقر الدم (انيميا) ، وخصوصا في المجموعة التى تلقت ثلاثة أضعاف الجرعة العلاجية ، ولوحظ ايضا نقص فى كرات الدم البيضاء في هذه المجموعات. على الرغم من الارتفاع الكبير لإنزيمات الكبد (ALP,ALT ,AST وايضا البيليروبين) لوحظ وجود انخفاض فى البروتين الكلى والزلال في المجموعات التى أخذت جرعة مضاعفة وجرعة ثلاثية من العقار بعد ٢٤ ساعة وأسبوع واحد من توقف العلاج ، من جهة أخرى فإن التغيرات الهستوباثولوجية أظهرت وجود تغيرات في أنسجة الكبد والكلى والطحال التى تزيد بزيادة الجرعة.وقد أظهرت الدراسة أيضا أن بقايا عقار الفلوبندازول والأيضات الخاصة به تتركز فى الكبد والكلى و لكن أعلى تركيز يوجد فى العضلات والتي تتزايد مع زيادة الجرعة٠مماسبق يمكننا ملاحظة أن الآثار السلبية ربما يعود إلى سمية العقار عند استخدامة بجرعات عالية لذا يجب مراعاة الجرعة وفترة سحب الدواء عند إستخدامة حرصا على سلامة المستهلك و الطيور٠