HEPATONEPHROTOXICITY OF COMBINED USE OF ENROFLOXACIN AND TOLTRAZURIL IN BROILER CHICKENS

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Abstract

This study was carried out on 80 apparently healthy unsexed, one day old broiler chicks (Hubbard strain) of nearly the same weight obtained from Miser Ismailia Poultry Company to unearth the possible untoward effects of enrofloxacin, toltrazuril and their concomitant use as a prophylactic drugs on liver and kidney functions that would portrayed as undesirable biochemical and histopathological effects. At the 21st day of age, the chicks were distributed randomly into four equal test groups named G1 (control), G2 (Enrofloxacin treated group), G3 (Toltrazuril treated group) and G4 (Enrofloxacin + Toltrazuril treated group). At 7th and 14th days post treatment, 10 birds from each group were scarified, blood samples were collected and serum samples were separated for biochemical analysis. Samples from kidneys and liver were obtained for histopathological examination. The obtained results of biochemical analysis revealed that the concurrent administration of both enrofloxacin and toltrazuril elicited a significant increase ($p < 0.5$) in estimated serum ALT, AST, uric acid and creatinine levels as compared to the control, enrofloxacin and toltrazuril treated groups. The histopathological examination showed congestion of liver, focal mononuclear cells infiltration, edema and severe necrosis of the hepatocytes. The kidney showed edema, focal mononuclear cells aggregation, cystic dilatation and necrosis of tubular and glomerular epithelium.

It could be concluded that concomitant use of enrofloxacin and toltrazuril as a prophylactic drugs could disturb liver and kidney functions as shown by biochemical findings and confirmed by histopathological results.

INTRODUCTION

In modern poultry industry, infectious diseases are a serious problem, they cause major economic losses. Therefore, various kinds of antibiotics and synthetic antimicrobials are extensively used for prevention and treatment. Moreover many antibiotics are used in high quantities not only for therapy and prevention of bacterial diseases, but also as antimicrobials growth promoters in poultry feed (Al-Mayah and Al-Ahmed, 2005). However, in certain countries 26% of the veterinary used antibiotics were intended for poultry broilers, resulting in yearly exposure of 430 mg of antibiotics /kg of year for poultry (Bogaard et al., 2000). Floroquinolones are of these antimicrobials which are widely used for therapy and chemoprophylaxis of

bacterial diseases. They are a class of compounds that comprise a large and expanding group of synthetic antimicrobials agents (Marilyn et al., 2006). Enrofloxacin considered one of the most commonly used of synthetic antimicrobials agents in poultry practice. It is rapidly bactericidal against a broad spectrum of aerobic and some facultative anaerobic bacteria, including strains that are resistant to many other antimicrobial agents' .It is also effective against some Gram-positive bacteria and mycoplsma (El-mas et al., 2007).

Coccidiosis is another serious problem in the field of poultry industry which caused by protozoan parasites in genus Eimeria (Long and Reid, 1982). It results in major economic losses due to reduced growth, poor flock uniformity, in efficient feed utilization and increased mortality (Mathis et al., 2003), so the control of coccidiosis is of critical importance. This was primarily achieved by the use of highly efficacious anticoccidials included in poultry feed (McDougald, 1982) or water (Mathis et al., 2003) for prevention and treatment. Toltrazuril is one of the highly efficacious commonly used. It is a symmetrical triazinetrione compound, it has been efficacious against all species of Eimeria infecting chickens (Haberkorn and Stoltefuss,1987 and Mehlhorn et al., 1988).Solubility and activity against all intracellular developmental stages of Eimeria infecting chickens (Mehlhorn et al., 1984) make this drug a highly effective anticoccidial .

Both antimicrobials and anticoccidials may be concomitantly used for prevention and treatment of bacterial diseases and coccidiosis in one broiler flock .However, 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 administered drugs (Rahal et al., 2008). A well knowledge problem associated with fuloroquinolones usage is the interaction between these antimicrobials and the metabolism of other drugs (Nakashi and Okuno,1990) .Therefor, the objective of the present study was planned to unearth the possible untoward effects of enrofloxacin, toltrazuril and their concomitant use as a prophylactic drugs on liver and kidney functions that would portrayed as undesirable biochemical and histopathological effects.

MATERIALS AND METHODS

1-Drugs:

A- Enrofloxacin (Enrotryl): Oral solution 10%.Egyptian company for chemicals and Pharmaceutical (ADWIA) S.A.E., 10th of Ramadan City, Egypt.

B- Toltrazuril (Baycox): Oral solution 2.5%, it was obtained from Bayer Company, Bayer, Leverkuson, Germany. Chemical name {3-methyl-4-(4-trifluromethyl thyo)-phenyle}-3-methyle-1,3,5-triazin-2,4,6 (1h,3h,5h)-trion.

2-Experimental chicks:

A total of 80 apparently healthy unsexed, one day old broiler chicks (Hubbard breed) of nearly the same weight were used in this study. They were obtained from Miser Ismailia Poultry Company. The chicks were kept in wire floored battery brooders under good hygienic condition. They were fed on a balanced commercial ration free from any medication and watered ad-libitum with a 24 hour light throughout the experimental period. At the 21st day of age, the chicks were distributed randomly into four equal test groups named G1 (control un treated), G2 (Enrofloxacin treated group), G3 (Toltrazuril treated group) and G4 (Enrofloxacin + Toltrazuril treated group). At 7th and 14th days post treatment, 10 birds from each group were scarified and blood samples were collected into clean and dry centrifuge tube for serum collection. The serum samples were separated by centrifugation at 300 r.p.m for 15 minutes and kept frozen at -20 C until analyzed. After collection of blood samples, the birds were sacrified and samples from kidneys and liver were obtained for histopathological examination.

3- Experimental design:

At the 21st day of age, the chicks were distributed randomly into four equal test groups (20 each) as shown in the Table (1).

Table 1. showing groups, number of chicks, drugs used, dose, duration of treatment, time of scarification and numbers of sacrificed chicks.

Groups	Number of chicks per group	Age of chicks at treatment	Drug, dose and duration of treatment				Time of scarification and numbers	
			Enrofloxacin	Duration day	Toltrazuril	Duration day	Time	No
G: 1 (Control)	20	At 21th of age	–	–	–	–	7th and 14th days post treatment	10 birds of each group were scarified at eat time
G: 2	20		1 ml/2 liter	3	—	–		
G: 3	20			–	1 ml/liter	2		
G:4	20		1 ml/2 liter	3	1 ml/liter	2		

4-Sampling:

At 7th and 14th days post treatment, 10 birds from each group were scarified and blood samples were collected into clean and dry centrifuge tube for serum collection. The serum samples were separated by centrifugation at 300 r.p.m for 15 minutes and kept frozen at -20 C until analyzed. After collection of blood samples, the birds were dissected and samples from kidneys and liver were obtained for histopathological examination.

5- Analysis:

A-Biochemical analysis:

The serum samples were used for determination of Aspartare aminotransferase (AST) and Alanine Aspartare aminotransferase (ALT) (Reitman and Frankel, 1957), serum total proteins according to (King and Wooton, 1982), albumen according to (Gassbaro et al., 1972), serum globulins were calculated as the difference between total proteins and albumen, uric acid according to (Henry et al., 1974) and creatinine according to (Folin, 1934).

B-Histopathological examination:

All experimental chickens were examined daily during the period of experiment. The clinical signs and post mortem change were recorded. Specimens from liver and kidneys were taken and fixed in 10% neutral buffered formalin then, dehydrated in different concentrations of alcohol, cleared in xylol then, embedded in paraffin wax. Tissue section of 5 microns thickness were prepared and stained with Hematoxylin and Eosin (H&E) then, examined under the light microscope (Bancroft et al., 1990).

6- Statistical analysis:

The results were reported as Mean I S.E. Statistical significance was determined using analysis of variance according to (Snedecor and Cochran, 1982). Mean were compared by Least Significance Difference (L S D) test at 0.5 significance level (Steel and Torrie, 1980).

RESULTS AND DISCUSSION

Biochemical findings:-

The results concerning the effect of orally administered toltrazuril, enrofloxacin and their combination on serum levels of ALT, AST, uric acid and creatinine in broiler chicks at (7th and 14th days) post treatment were summarized in Table(2). Concerning serum ALT and AST levels, it was cleared that, enrofloxacin treated chicks revealed a significant increase ($p < 0.5$) in estimated ALT and AST levels at (7th and14th days) post treatment as compared to the control and toltrazuril treated groups. Increase in serum ALT and AST activities were depending on hepatocellular damage (San Martin-Nunez et al., 1988). Our findings seem conceivable to be attributed to disturbances in liver functions resulted from the use of the drug. These results coincide with those previously recorded by (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), Rasha (2008) and El-Ghoneimy et al., (2008). Moreover, these results were supported by the obtained results of histopathological examination of hepatic tissues of treated chicks in our study which revealed degenerative changes in the hepatic cells and acute toxic hepatitis. Regarding serum ALT and AST levels, it was cleared that toltrazuril treated birds showed a non significant increase ($p < 0.5$) in estimated serum ALT and AST levels at (7th and14th days) post treatment as compared to the control group. This results were confirmed by Elen (1993), Abdel-Alem and Mohi (2003). The concurrent administration of both toltrazuril and enrofloxacin elicited a significant increase ($p < 0.5$) in estimated serum ALT and AST levels at (7th and14th days) post treatment as compared to the control, enrofloxacin and toltrazuril treated groups. There were no available literatures explain the therapeutic outcome of concurrent use of both enrofloxacin and toltrazuril 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., 2008). This may be attributable to interactions that occur within the body which might be of pharmacokinetic or pharmacodynamic type. Concerning serum uric acid and creatinine levels, it was recorded that enrofloxacin treated group revealed a significant increase ($p < 0.5$) in estimated serum uric acid at (7th days) and creatinine levels at (7th and14th days) post treatment as compared to the control and toltrazuril treated groups. 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 our study. These results are in accordance with Khodary and El-Sayed, (1997) who 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. Regarding serum uric acid and creatinine levels, it was noticed that toltrazuril treated birds elicited non significant increase ($p < 0.5$) in determined serum uric acid and creatinine levels at (7th and14th days). These results were confirmed by Elen (1993). The concurrent administration of both toltrazuril and enrofloxacin elicited a significant increase ($p < 0.5$) in estimated serum uric acid at (7th days) as compared to the control and toltrazuril treated groups and creatinine levels at (7th days) post treatment as compared to the control, toltrazuril and enrofloxacin treated groups and at (14th days) as compared to the control and toltrazuril treated groups. There were no available literatures explain the therapeutic outcome of concurrent use of both enrofloxacin and toltrazuril 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., 2008). This may be attributable to interactions that occur within the body which might be of pharmacokinetic or pharmacodynamic type. The 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 both enrofloxacin and /or toltrazuril on kidney. This explanation confirmed by the obtained histopathological alterations in the kidneys in this study. The results concerning the effect of orally administered enrofloxacin,

toltrazuril and their combination on serum levels of total proteins, albumin and globulin in broiler chicks at (7th and 14th days) post treatment were summarized in Table(3). Enrofloxacin treated chicks showed a significant decrease in estimated serum levels of total proteins, albumin and globulin at (7th days), meanwhile non significant change at (14th days) post treatment as compared to the control. These findings seen conceivable to be attributed to disturbances in liver functions as a result of hepatic damage caused by direct effect of enrofloxacin or its metabolite on liver. This explanation could be confirmed by the obtained histopathological changes in the liver in our study. Regarding serum total proteins, it was cleared that toltrazuril treated birds showed a non significant increase ($p < 0.5$) in estimated serum levels of total proteins, albumin and globulin at (7th and 14th days) post treatment as compared to the control. The concurrent administration of both toltrazuril and enrofloxacin elicited a significant decrease ($p < 0.5$) in estimated serum total proteins and albumin at (7th and 14th days) post treatment as compared to the control and toltrazuril and enrofloxacin treated groups. The liver is responsible for a great production of plasma proteins (Cole, 1986). In the glow of this notion, the decrease in total proteins and albumin levels seen conceivable to be attributed to damage of the liver of treated birds caused by the direct effect of both enrofloxacin and /or toltrazuril on liver.

Histopathological findings:-

The liver of enrofloxacin (1ml / 2 liters) treated chickens showed congestion, edema, necrosis of hepatocytes and focal lymphocytic infiltration at 7th day post administration (Plate I: 1 and 2). showed edema, congestion of hepatic blood vessels and necropiotic changes of hepatocytes at 14th day post administration (Plate I: 3 and 4). The kidney showed edema and severe necrosis of tubular and glomerular epithelium of at 7th day post administration (Plate II: 5). Edema, tubular nephrosis and necrosis at 14th day post administration (Plate II: 6). These results are in full agreement with Helal et al., (1995); Ramadan (1996) and Magdy and Ahmed (1998)
The liver of toltrazuril (1ml / liter) treated chickens showed congestion, vacuolar degeneration and necrosis of some hepatocytes and dilatation of blood sinusoids at 7 th day post administration (Plate II: 7). Edema, necrosis, degenerative changes in hepatocytes and haemorrhage at 14th day post administration (Plate II: 8). This result is in full agreement with Elen (1993) and Abdel-Alem and Mohi (2003). Kidney of Toltrazuril (1ml/liter) treated chickens slaughtered at 7th day post administration showing edema, nephrosis and some scattered mononuclear cells (Plate II: 9). Slight edema and tubular nephrosis at 14th day post (Plate II: 10). This result is in coincided with Elen (1993) and Abdel-Alem and Mohi (2003).

The liver in enrofloxacin (1ml / 2 liters) + toltrazuril (1ml / liter) treated chickens showed congestion, focal mononuclear cells infiltration, edema and severe necrosis of the hepatocytes at 7th day post administration (Plate III: 11). Congestion, edema and severe necropiotic changes of the hepatocytes at 14th day post administration (Plate III: 12). The kidney showed edema, focal mononuclear cells aggregation and necrosis of tubular and glomerular epithelium at 7th day post administration (Plate IV: 13). Cystic dilatation and necrosis of glomerular and tubular epithelium at 14th day post administration (Plate IV: 14). The results 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 toltrazuril in treated chicks. This may be attributable to interactions that occur within the body which might be of pharmacokinetic or pharmacodynamic type. This explanation was confirmed by the obtained biochemical findings in the present study.

Conclusion: It could be concluded that concomitant use of enrofloxacin and toltrazuril as a prophylactic drugs could disturb liver and kidney functions as shown by biochemical findings and confirmed by histopathological results.

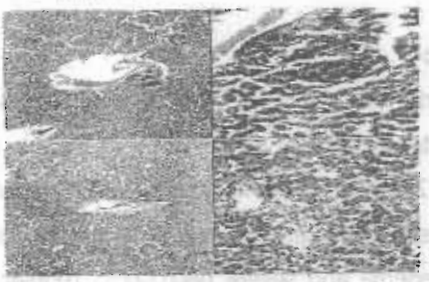

Plate I:

(1): Liver of Enrofloxacin (1ml/2liter) treated chickens slaughtered at 7th day post administration showing congestion, edema, necrosis of hepatocytes and focal lymphocytic infiltration (H & E Stain, X 250).

(2): Higher magnification of (1) showing congestion, edema, necrosis of hepatocytes and focal lymphocytic infiltration (H & E Stain, X 400).

(3): Liver of Enrofloxacin (1ml/2liter) treated chickens slaughtered at 14th day post administration showing edema, congestion of hepatic blood vessels and necropiotic changes of hepatocytes (H & E Stain, X 250).

(4): Higher magnification of (3) showing edema, congestion of hepatic blood vessels and necropiotic changes of hepatocytes (H & E Stain, X 400).

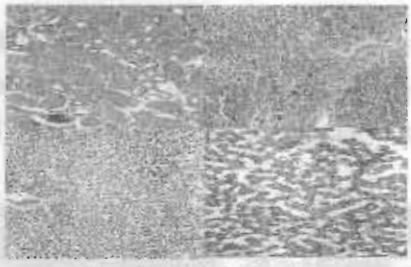

Plate II:

(5): Kidney of Enrofloxacin (1ml/2liter) treated chickens slaughtered at 7th day post administration showing edema and severe necrosis of tubular and glomerular epithelium (H & E Stain, X 250).

(6): Kidney of Enrofloxacin (1ml/2liter) treated chickens slaughtered at 14th day post administration showing edema, tubular nephrosis and necrosis (H & E Stain, X 100).

(7): Liver of Toltrazuril (1ml/liter) treated chickens slaughtered at 7st day post administration showing congestion, vacuolar degeneration and necrosis of some hepatocytes and dilatation of blood sinusoids (H & E Stain, X 250).

(8): Liver of Toltrazuril (1ml/liter) treated chickens slaughtered at 14th day post administration showing edema, necrosis, degenerative changes in hepatocytes and haemorrhage (H & E Stain, X 250).

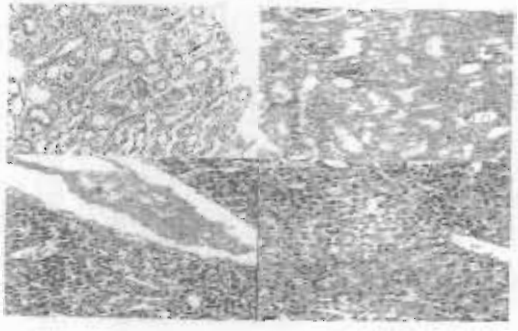

Plate III:

(9): Kidney of Toltrazuril (1ml/liter) treated chickens slaughtered at 7th day post administration showing edema, nephrosis and some scattered mononuclear cells (H & E Stain, X 250).

(10): Kidney of Toltrazuril (1ml/liter) treated chickens slaughtered at 14th day post administration showing slight edema and tubular nephrosis (H & E Stain, X 250).

(11): Liver of Enrofloxacin (1ml/2liter) + Toltrazuril (1ml/liter) treated chickens slaughtered at 7th day post administration showing severe congestion, focal mononuclear cells infiltration, edema and severe necrosis of the hepatocytes (H & E Stain, X 400).

(12): Liver of Enrofloxacin (1ml/2liter) + Toltrazuril (1ml/liter) treated chickens slaughtered at 14th day post administration showing severe congestion, edema, pyknosis and severe necropiotic changes of the hepatocytes (H & E Stain, X 400).

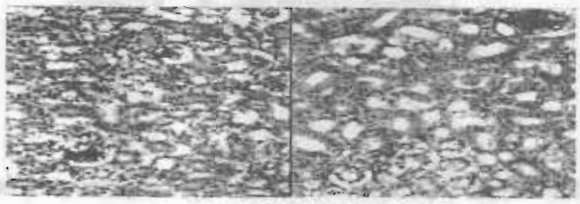

Plate IV:

(13): Kidney of Enrofloxacin (1ml/2liter) + Toltrazuril (1ml/liter) treated chickens slaughtered at 7th day post administration showing edema, focal mononuclear cells aggregation and necrosis of tubular and glomerular epithelium (H & E Stain, X 250).

Figure (14): Kidney of Enrofloxacin (1ml/2liter) + Toltrazuril (1ml/liter) treated chickens slaughtered at 14th day post administration showing cystic dilatation and necrosis of glomerular and tubular epithelium (H & E Stain, X 250).

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التسمم الكبدى الكلوى نتيجة الاستعمال المتزامن لكل من الانروفلوكساسين والتولترازوريل فى بدارى التسمين

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١ - *كلية الطب البيطرى- قنا- جامعة جنوب الوادى- مصر.*
٢- *معهد بحوث صحة الحيوان بالأسماعيلية .*

قد أجريت هذه الدراسة على عدد ٨٠ كتكوت من بدارى التسمين عمر يوم واحد سليمة ظاهريا وغير مجنسة من (سلالة هبرد) التي تم الحصول عليها من شركة مصر الاسماعيلية للدواجن وذلك لكشف الآثار المحتملة الغير مرغوب فيها نتيجة الإستخدام المتزامن لكل من عقارى الإنروفلوكساسين و التولترازوريل كأدوية وقائية على وظائف وظائف الكبد والكلى من خلال الفحوصات البيوكيميائية والهستوباثولوجية. وقد وزعت الكتاكيت عشوائيا عند عمر ٢١ يوم إلى أربع مجموعات متساوية المجموعة الأولى ضابطة، المجموعة الثانية معالجة بالإنروفلوكساسين، المجموعة الثالثة معالجة بالتلترازوريل والمجموعة الرابعة معالجة بكلاهما معاً. وفي اليوم السابع والرابع عشر بعد العلاج، قد تم ذبح عدد ١٠ طيور من كل مجموعة، تم جمع عينات الدم و فصل المصل للتحليل البيوكيميائى. وقد تم الحصول على عينات من الكلى والكبد للفحص النسيجي. وقد كشفت نتائج التحليل البيوكيميائى أن الاستخدام المتزامن لكل من عقارى الإنروفلوكساسين و التلترازوريل فى بدارى التسمين أظهر زيادة معنوية في مستوى انزيمات الألانين و الأسبرتيت ترانسفيريز، الكرياتينين و حمض البوليك فى مصل الدم بالمقارنة مع المجموعاة الضابطة، المجموعة المعالجة بالإنروفلوكساسين والمجموعة المعالجة بالتلترازوريل.

وقد أظهر الفحص النسيجي للكبد والكلى احتقان الكبد، تسلل خلايا وحيدات النوى، ارتشاح ونخر شديد في خلايا الكبد .وأظهرت الكلى ارتشاح، تجميع الخلايا وحيدات النوى ونخر بالنسيج المبطن للأنيبيبات الكلوية والكبيبيات. وقد خلصت هذه الدراسة إلى أن الاستخدام المتزامن لعقارى الإنروفلوكساسين و التلترازوريل كأدوية وقائية يمكن أن تعيق وظائف الكبد والكلى كماهو واضح من نتائج التحليل البيوكيميائى، وأكدته نتائج الفحص النسيجي .