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Pharmacological studies on Ceftiofur in sheep

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ABSTRACT

This work was done on twenty young male and female lambs (15-60 days old) in a special sheep grazing herds in Dakahlia governorate. Lambs were divided into two groups; each one has ten animals. The first group non-vaccinated, kept as a control group without any interference by any medication. The second group lamb was injected with ceftiofur (2mg/kg B.W) s/c at posterior aspect in the middle third of ear as single dose. Results revealed a significant decrease in total erythrocytic count, hemoglobin content, total leukocytic count, lymphocyte count, monocyte count, eosinophil count, globulin, ALT, total protein, Albumin ;creatinine and urea level. On other hand, results recorded a significant increase in PCV, MCH, MCHC, AST, neutrophil count and platelets count in ceftiofur treated group compared to control one.

1. INTRODUCTION

Continuous breeding means lambing during all the year in the flock, poor cleaning and absence of veterinary supervision lead to accumulation of pathogens and recharge of the fecal-oral cycle (Coop and Wriarth, 2000). Gathering of lambs in small areas and poor hygiene lead to diseases spreading (Causape et al., 2002).

Diarrhea is called scour in livestock, it was described as a frequent, fluidity, blood or mucous and abnormal color may be included; however, it is so hard to surely detect the infectious microorganism by naked eye without laboratory examination. Diarrhea is a clinical entity causes serious economic losses as it may lead to high mortality, weight loss or even retard growth in different animals and even in human. It is caused by a combination of many risk factors (Bastawerous et al., 2001 and Gwyther et al., 2012).

Salmonella infection is a serious public health hazard; it has great effect economically all over the world because of the payments associated with lifesaving, eradication, control, treatment and curing strategy of diseases (Crump et al., 2004). Salmonella as well as Campylobacter are the most foodborne pathogens isolated, especially in dairy animal's products and poultry (Silva et al., 2011).

Higgins et al. (2005) reported that, diarrheagenic *Escherichia coli*, which include enterohemorrhagic and *E. coli* enteropathogenic *E. coli* are main cause of diarrheal diseases in sheep. Enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), (EPEC) and (EHEC) are major ones. They differ in their

epidemiology, pathogenicity and their serotypes (Mora et al., 2012).

Enterotoxemias in sheep and goat is important enteric disease caused by *Clostridium perfringens* which is a normal inhabitant organism in intestine of many animals, even humans, when changing occur in environmental gut by any risk factor, *C. perfringens* proliferates and secrete potent toxins which absorbed into the general circulation or act locally causing harmful effects on the animal body. (Uzal et al., 2008).

In goats and sheep, antibiotics are used in large scale for diarrhea treatment, new generations of virulent and resistant type of bacteria are produced because of incomplete course of treatment, continuous use of antibiotics against diarrhea (Marshall et al., 1990).

Ceftiofur is third generation cephalosporin, broad spectrum antibiotic. Ceftiofur is very good for respiratory disease in small, large ruminants and horses and is recommended for foot rot and metritis in cattle, also for turkey early mortality infections and day-old chicks (Hornish and Kotarski, 2002).

Presence of bulky iminomethoxy side chain in ceftiofur made it have a good resistance to be inactivated by β -lactamase produced by some bacteria (Klein and Cunha, 1995 and Dolhan, et al 2014).

Our study was performed to detect the efficacy of ceftiofur in treatment of diarrhea in lambs and to study its

effects on some hematological and biochemical parameters in treated lambs.

2. MATERIALS AND METHODS

2.1-Drug

Ceftiofur crystalline free acid

Product name: EXCEDE®

A sterile suspension 200mg/ml, was obtained from zoites company,USA./ Pizer,Egypt.

Dose:

The safe dose is 2mg/kg B.W subcutaneously at the third middle in base of ear. (Salmon et al., 1996)

2.2. Experimental lambs:

The lambs under our experiment were selected after long time of survey (6/2016 – 1-2019) in different sheep grazing herds at Dakahlia governorates; our survey was done on 20 lambs at 15-60 days old age.

2.3.Experimental design:

This work was done on twenty young lambs (15-60) days old in a special sheep grazing herds at Dakahlia governorate. Lambs were divided into two groups; each one has ten animals .The first group non-vaccinated, kept as controlled group without any interference by any medication. The second group lamb was injected with ceftiofur (2mg/kg B.W) subcutaneously at posterior aspect in the middle third of ear as single dose.

2.4. Sampling:

Two samples of blood were collected from all lambs jugular vein at zero day, 7th and 14th day. The first blood samples were collected on Wassermann tube containing EDTA (0.5 mg 2ml blood) for hematological parameters studies while; the second samples were collected in Wassermann tube without anticoagulant and are allowed to be clotted at room temperature. Then the sera were separated by the centrifuge at 3000 round per minute for 15 minutes. The sera were collected in 1.5ml eppendrofs and kept frozen at minus twenty degree for biochemical studies.(stoffregen et al., 1997)

2.5.Hematological studies:

Were carried out using fully automated cell counter (Mindary BC-2800).Mindary auto hematological BC- 2800 analyzer is an automatic hematology analyzer that used for in vitro diagnosis as CBC test.

2.6. Serum Biochemical Analysis:

Biochemical serum analysis of total protein, albumin, AST, ALT, urea, creatinine were carried out using automatic biochemical analyzer.

(A)Liver function tests:

Determination of Total Protein :(Gornal et al., 1949).

Albumin: (Doumas et al., 1981).

Serum globulin calculation: (Doumas and Biggs, 1972).

serum Transaminases (ALT) and (AST): (Reitman and Frankel,1957).

(B) Kidney function tests:

Creatinine serum: (Bartles et al.,1972).

Urea :(Fawcett and scott;1960).

2.7. Statistical analysis:

Data obtained in this study were statistically analyzed by one way (ANOVA), using SPSS computer program (Version. 20) and least significant difference (LSD) as described by Snedecor and Cochran (1981).

3. RESULTS

Table (1): The effect of single subcutaneous dose of ceftiofur (2mg/kg body weight) on some hematological parameters in lambs.(Mean ± S.E).

Item	Group	Zero	7 th	14 th
RBCs (x 10 ⁶ /ml)	Control	5.86±0.51	6.74±0.42	7.27±0.35
	Treated	3.95±0.26*	3.98±0.19*	3.97±0.12*
Hb(g / dl)	Control	12.34±0.31	11.24±0.22	10.39±0.19
	Treated	9.20±0.37*	6.73±0.16*	7.19±0.24*
PCV %	Control	17.35±0.89	15.43±0.81	14.06±0.84
	Treated	13.71±0.69*	13.97±0.80*	13.37±0.81
MCV (fl)	Control	35.46±0.59	36.42±0.56	34.01±0.41
	Treated	37.54±0.70*	36.44±1.17	35.06±0.45
MCH (pg)	Control	14.72±0.51	13.84±0.43	12.60±0.37
	Treated	24.08±1.56*	20.19±0.87*	23.64±0.69*
MCHC (%)	Control	35.94±2.03	41.15±2.07	44.41±1.98
	Treated	50.84±7.42*	42.95±2.07	42.90±2.66
WBCs (× 10 ³ /ml)	Control	7.51±0.52	8.76±0.45	9.69±0.48
	Treated	10.34±0.52*	7.52±0.59*	6.43±0.49*
Neutrophil (%)	Control	26.8±1.20	27.00±1.09	26.00±1.09
	Treated	27.30±1.72	30.0±1.42*	27.40±1.94

Lymphocyte (%)	Control	65.0±1.60	67.33±1.45	69.30±1.47
	Treated	65.7±2.08	64.62±2.51*	69.2±1.54
Monocyte (%)	Control	3.75±0.44	3.1±0.35	2.88±0.27
	Treated	3.70±0.41	2.98±0.51	2.20±0.24*
Basophil (%)	Control	1.35±0.15	0.57±0.19	0.53±0.17
	Treated	0.90±0.20*	0.60±0.22	0.50±0.16
Eosinophil (%)	Control	3.10±0.50	2.00±0.44	1.29±0.35
	Treated	2.4±0.46*	1.80±0.35	0.70±0.15*
Platelets (n × 10³ /ml)	Control	523.50±30.40	494.30±31.52	461.70±31.47
	Treated	545.10±27.10	595.80±10.82*	511.40±32.15

*significant at (p<0.01)

The table 1 showed:

- a significant decrease in total erythrocytic count in ceftiofur treated group at 0,7th, 14th day after treatment.
- A significant decrease in hemoglobin content count in ceftiofur treated group at 0,7th, 14th day after treatment related to control group.
- A significant increase in packed cell volume in ceftiofur treated group at 0,7th, non-significant change at 14th day after treatment related to control group.
- A significant decrease in mean corpuscular volume (mcv) at zero, 7th day post treatment and non-significant change at 14th day.
- A significant increase in mean corpuscular hemoglobin volume (mch) at 0,7th, 14th day post treatment.
- A significant increase in mean corpuscular hemoglobin concentration at 0 day and non-significant change at 7th,14th day post treatment.
- A significant increase in total leucocytic count at 0 day, while significant decrease at 7th, 14th day post treatment.
- Non- significant change in neutrophils at 0,14th day, while significant increase at 7th day posts treatment.
- Non-significant change in lymphocytes at 0,14th day,while significant decrease in 7th post treatment.
- Non- significant change in monocytes at 0 ,7th while significant decrease in 14th day.
- A significant decrease in basophil at 0 day, while non-significant change at 7th , 14th day post treatment.
- A significant decrease in esinophils at 0,14th day while non -significant change at 7th day.
- Non-significant change in platelets at 0,7th day while significant increases at 7th day post treatment.

Table (2): The effect of single subcutaneous dose of ceftiofur (2mg/kg body weight) on some biochemical parameters in lambs.

(Mean ± S.E) n=10

Item	Group	Zero	7 th	14 th
Total protein (g/dl)	Control	6.17±0.19	6.78±0.15	7.79±0.13
	Treated	6.36±0.45	5.91±0.26*	7.08±0.30
Albumin (g/dl)	Control	2.45±0.15	3.28±0.17	3.81±0.20
	Treated	3.18±0.12*	2.40±0.07*	3.34±0.30
Globulin (g/dl)	Control	3.69±0.28	3.49±0.27	4.19±0.17
	Treated	3.17±0.47	3.50±0.26	3.73±0.48*
ALT (IU/L)	Control	23.85±1.17	28.77±1.23	31.91±1.19
	Treated	22.91±2.77	15.64±1.11*	17.50±0.74*
AST (IU/L)	Control	97.86±5.11	110.41±4.58	123.78±4.95
	Treated	118.75±4.67*	106.85±10.63	118.39±6.55
Creatinine (mg/dl)	Control	1.63±0.062	1.65±0.059	1.81±0.41
	Treated	1.45±0.06*	0.85±0.030*	0.70±0.063*
urea (mg/dl)	Control	1.30±0.12	2.55±0.16	3.64±0.17
	Treated	1.66±0.14	1.40±0.21*	1.00±0.07*

*significant at (p<0.01)

Table 2 showed:

- Significant decrease in total protein at 7th day, while non-significant change at 0 ,14th day post treatment.
- Significant increase in albumin at 0 day, while significant decrease at 7th day, no change at 14th day posts treatment.
- Significant decrease in globulin at 14th day, while non-significant change at 0, 7th day post- treatment.
- Non- significant change in ALT at 0 day,while significant decrease at 7th,14th day post treatment.
- Significant increase in AST at 0 day, while non-significant change at 7th, 14th day post-treatment.
- Significant increase in creatinine at 0 day, while significant decrease at 7th, 14th day post-treatment.
- Non-significant change in urea at 0 day, while significant decrease at 7th ,14th day post treatment.

4. DISCUSSION

In young domestic animals, diarrhea is life threatening although its etiology is not well revealed as several agents may be contributed, moreover, many of these agents can affect the animal body without introducing apparent clinical signs (Smith and Sherman 1994).

In lambs *Escherichia coli*, rotavirus, coronavirus and *Cryptosporidium* species are listed as the most frequent micro-organisms causing diarrhea (Fassi-Fehri et al., 1988).

Salmonella and *Clostridium perfringens* species play vital role in sheep diarrhea (Nagy et al., 1987)

The obtained results documented a significant decrease in hemoglobin content and total erythrocytic count in ceftiofur treated group at zero, seventh and fourteenth post treatment compared to control group (Table 2).

The present result agrees with those of Wahid et al;(1988) who found a significant decrease in the values of HB and TEC in post treatment with ceftiofur administration as single subcutaneous dose (2mg/kg BW) in treated diseased cows with metritis.

These result disagree with that of Kishanrao(2016) who found a significant increase in hemoglobin and total erythrocytic count in diarrheic bufflo calves treated with

cefquinome. And Modi et al., (2013) also detected no significant differences in RBCS and hemoglobin concentration after administration of marbofloxacin in sheep (Table 2).

Barger(2003) mentioned that the Significant decrease in Hb content might attributed to reduction synthesis of red blood cells or reduced heme biosynthesis in bone marrow or due to increased rate of its destruction. The improper synthesis of hemoglobin may be caused by increasing hemolysis or decrease bone marrow activity and so far, hypochromic anemia.

Our data recorded a significant increase in MCH, MCHC, PCV in post treatment with ceftiofur administration as single subcutaneous dose (2mg/kg BW) (Table.2). These results were agreed with data obtained by Ahmad et al;(2003) who revealed increase of same parameters in crossbred cows with endometritis. Moreover Ishak et al., (2008) who recorded higher PCV MCH, and MCHC in marbofloxacin-treated cats (2.75 mg/kg PO daily for 14 days) infected with *Mycoplasma haemofelis*.

On contrary, these results were disagree with those of Bhuyan et al;(2017) and Kumar et al (1985) who found a decrease in MCH,MCHC,PCV in cows infected with metritis which treated with ceftiofur.

The diarrheic lambs showed a significant improvement and rapid recovery from these alterations after treatment by ceftiofur. The present data showed a significant increase of total leukocytic count in ceftiofur treated group at zero day then decrease at seventh and fourteenth post treatment and return to normal percent.

Also the study recorded a significant increase in neutrophil percent in ceftiofur treated group at seventh day post treatment compared to control group (Table 2). As well recorded a significant decrease of lymphocyte percent in ceftiofur treated group at at seventeenth day post treatment compared to control group. And also significant decrease in monocytes at fourteenth day and decrease in basophil at zero day, decrease in eosinophil percent in zero, seventh day.(Table 2)

In this aspect Vipul et al,(2017) found significant decline in the values monocyte in post treatment with marbofloxacin administration alone (5 mg/kg of body weight for 5 days) when compare to untreated group of the same parameters in piperine pretreated group II ($p < 0.05$). Furthermore Shpigel and Schmid (1997) reported a significant decrease in total leucocytic count, serum calcium and phosphate with cefiquinom treated cows with mastitis. Also Shams, (2017) showed a significant decrease in monocyte marbofloxacin (2mg/kg) with flunixin meglumine (2.2mg/kg) in treated mastitic cattle and agreed with those of Sarma(2007) who reported that increase neutrophil percent in infected cows than healthy ones. Illhwa et al;(2005) revealed increase in neutrophil percent in

Cows with metritis. Anan(2017) found a decrease in lymphocytes percent in cows treated with ceftiofur. Javid et al;(2004) also detected a decrease in lymphocyte percent in cow treated with ceftiofur.

The obtained results Disagreed with those of Shams, (2017) who recorded a significant increase in total leucocytic count lymphocyte percent in marbofloxacin treated mastitic cows (2mg/kg) with tolfenamic acid(2mg/kg). Moreover Ayat(2018) detected a significant increase in monocyte percent in marbofloxacin treated group at seventh and fourteenth days post treatment compared to control group.

This might be attributed to extravastion of lymphocyte to the site of infection (Benjamin 1985) who observed that leukocytopenia caused release leukocytosis induced factor which stimulate the bone marrow for maximum production of neutrophil.(Kumar et al,1985)

Our result evaluated a significant increase in platelet count in ceftiofur treated group at seventh day of treatment compared to the control group (Table 2).

This results Agree with Anan (2017) who noticed a significant increase in platelets in treated cows with ceftiofur .

These results disagree with these of Zhixin Lei et al., (2018) who recorded a decrease in platelet in the 6 and 10 mg/kg treatment groups of peagle dog on day 14 and 40 compared to control group.

A significant decrease in total protein, albumin and globulin in ceftiofur treated group at zero ,seventh and fourteenth day after treatment in comparsion with the control group. (Table3).

The obtained results agree with those of Maden et al.,(2001) and with Ayat(2018) who reported decrease in albumin and total protein in cows treated with marbofloxacin.

The obtained data are disagree with those of Mahmood and Hussein (2013) who found a non-significant change in total protein, albumin and globulin following daily

Intramuscular administration marbofloxacin (2 mg/kg) and trovafloxacin (3 mg/kg) for five days in sheep.

The lack of albumin may occur due to prolonged diarrhea which results in liver disorders (Radhakishan 1991)

ALT and AST activities are non-specific intracellular enzymes, which widely present in many organs especially liver. Their using is wide-ranging from broadcasting of liver disease to observing side effects of medication to determine reactions to treatment. The cellular damage and rupture of plasma membrane evoked the activities of these enzymes in serum (Wang et al., 2006).

This work reflected a significant decrease in serum alanine transaminase (ALT) activity in ceftiofur treated group at third day post treatment, Also detected a significant increase in serum aspartate transaminase (AST) activity in ceftiofur treated group at zero and third days post treatment . zero ,seventh and fourteenth days post treatment compared to the control group (Table 3).

This result is supported also by the findings reported by Anan (2017). Who mentioned that increased serum transaminase activities suggest hepatocellular damage.Although these results disagree with those of Ayat (2018) who reported an increase in AIT activity.

Our result documented a significant increase in creatinine level in ceftiofur treated group at zero day then decrease at seventh, fourteenth compared with control animals (Table 3). Elevated level of creatinine in serum is known to reflect the

state of glomerular filtration and indicate kidney disease (Coles, 1974).

A significant increase also detected in urea level at zero, then decrease at seventh and fourteenth days with ceftiofur comparing with the control group (Table 3).

The significant increase in serum urea nitrogen and creatinine in the present study was due to dehydration as a consequence of diarrhea. The hypovolemia due to dehydration results in concentration of the plasma solutes with relation to increase in both parameters.

The rise of urea concentrations is relatively more pronounced than that of creatinine concentrations in azotemia caused by dehydration (Stockham et al., 2002).

Our data disagreed with those of Anan(2017) who observed no change in urea level after treatment of ceftiofur in infected cows. On the opposite side Hanly(2017) reported an increase in urea level after cefiquinom in rats.

On other side this result disagrees with those of Patel et al., (2014) who reported that following single intravenous administration of marbofloxacin (2 mg/kg) the values of alanine aminotransferase was significantly reduced after drug administration in sheep but within the normal clinical range. Bhavsar et al., (2004) determined Other fluoroquinolones like ciprofloxacin when given repeated in calves at intra muscular dose in calves did not cause any significant alteration in the values of (ALT, AST, creatinine and urea level).

Conclusion

From this study it could be concluded that, a single subcutaneous injection of ceftiofur at the dose rate (2mg/kg BW) in diarrheic lambs was found to have highly significant effect on hematological and biochemical parameters of diarrheic lambs and consider a corner of stone in treatment and control of diarrhea caused by bacterial infection.

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