



# Effects of eprinomectin administration on apoptosis, acute phase response and antioxidant status in cattle

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## ABSTRACT

Eprinomectin is a broad spectrum endectocides used against gastrointestinal, pulmonary nematodes and ectoparasites in cattle. The main objective of the present study was to investigate effects of eprinomectin in cows following subcutaneous and pour-on administrations; on serum DNA apoptosis, acute phase response, Total Antioxidant Status (TAS), total protein, creatinine, urea levels, and AST, ALT and GGT activities. Ten Holstein cows were divided into two groups. Group 1 received subcutaneous (0.2 mg/kg) and group 2 received pour-on (0.5 mg/kg) administration of eprinomectin. Blood samples were collected from vena jugularis prior to and following the drug administration at intervals of 36 hrs, 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>nd</sup> and 20<sup>th</sup> days, respectively. Samples were centrifuged at 2500 g for 15 minutes and separated sera stored at -20°C. Results showed that the eprinomectin application decreases the sera levels of acute phase proteins. Statistically significant increase was observed in antioxidant capacity ( $P < 0.05$ ) and total protein ( $P < 0.01$ ). However, there was non-significant increase in apoptosis rate. No remarkable alterations were observed in AST, ALT and GGT activities including urea and creatinine levels. Results showed that the eprinomectin application reduces the sera levels of acute phase proteins (ceruloplasmin and sialic acid) in cows. However, statistically significant increase was measured in antioxidant capacity ( $P < 0.05$ ) and total protein ( $P < 0.01$ ) levels. It could be concluded from the study that eprinomectin do not have adverse effects on liver and kidney.

**Key words:** Acute phase proteins, Antioxidants, Apoptosis, Eprinomectin.

## INTRODUCTION

Eprinomectin, belongs to avermectins, subgroup of macrocyclic lactone family and entitled "endectocide" out of effecting internal and external parasites (Shoop *et al.*, 1996).

Avermectins with a similar mode of action-ivermectin, shows signs of paralysis and ataxia in their behavior (Taylor, 2001). However, little is known about the apoptotic effect and on acute phase reaction of Avermectins.

Avermectins could induce oxidative damage to the brain tissue and serum (Wang and Li, 2008; Wang *et al.*, 2009). Apoptosis could be induced by endogeneous and exogeneous factors (Aksit and Bildik, 2008; Cotran *et al.*, 1999; Karwatsky *et al.*, 2003, Mattson and Chan, 2003; Prabhavathy and Palanivel, 2015). Following usage of avermectins at treatment doses a rise in plasma nitric oxide levels was reported (Atakisi *et al.*, 2009). Furthermore, high concentration of avermectins can cause apoptosis in mammalian neurons (neuron mitochondria of King pigeons) (Wang and Li, 2008; Wang *et al.*, 2009).

It has been reported that lipid peroxidation occurs due to increased free radicals in helminthes and protozoa infected hosts and parasitic infections cause depletion of antioxidants. (Gameel, 1982; Sarin *et al.*, 1993). Free radicals are produced in the body as by products of normal metabolism and as a result of exposure to radiation and some environmental pollutants. Free radicals are normally neutralized by efficient systems in the body that include the antioxidant defense system (Kabu *et al.*, 2015; Sardesai, 1995). Low levels of antioxidants in blood reflect oxidative damage caused by free radicals (Joreno, 1990; Kanbur

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*et al.*, 2008; Noori *et al.*, 2018). Increases in plasma sialic acid levels may be attributed to the elevated concentrations of acute phase proteins (Baspinar and Serpek, 1993; Çorum and Kart, 2017; Sydow *et al.*, 1988).

The aim of the present study was to investigate effects of recommended doses of eprinomectin on apoptosis, acute phase response, total antioxidant status (TAS), total protein, creatinine, urea levels and AST (aspartate aminotransferase), ALT (alanine aminotransferase) and GGT (gamma glutamyl transferase) activities in cows.

## MATERIALS AND METHODS

3,5-5 years old, 250-360 kg weight, 25<sup>th</sup> day of the dry off and non-pregnant ten Holstein cows were used. Randomly selected cows were divided into two groups. Diets consisted of 50% forage and 50% concentrate and were formulated to contain 16.25% protein in each trial. Eprinomectin was

administrated subcutaneously (0.2 mg/kg) (Eprecis Injectable Solution, 1% w/v, Ceva, Istanbul, Turkey) in the first group (5 cows) and pour-on (0.5 mg/kg) (Eprinex Pour-on, 0.5% w/v, Merial, Istanbul, Turkey) in the second group (5 cows). Blood samples were collected from vena jugularis prior to drug administration (Control groups) and after administration at intervals of 36<sup>th</sup> hour, 3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup> and 20<sup>th</sup> days, respectively. Then, these samples were centrifuged for 15 minutes at 2,500 g and serum samples put into plastic tubes and stored at -20°C. There was no drug administration during the process. They were fed with hay, alfalfa, concentrated feed and *ad libitum* water. The cows were monitored daily for health status.

Measurement of serum apoptotic DNA fragmentation (free and circulating in blood) was done with commercially available ELISA kit (Roche Diagnostics, Mannheim, Germany). Serum total sialic acid was measured spectroscopically using Warren (1959)'s thiobarbituric acid method (Shimadzu UV 1800). Serum ceruloplasmin levels were determined as per Sunderman and Nomoto (1970). The levels of total antioxidant activity (Rel Assay Diagnostics, Gaziantep, Turkey), total protein, creatinine, AST, ALT, urea and GGT were done on biochemical autoanalyzer (Sinnova D280, China) using commercially available kits (Archem Diagnostic Ind. LTD, Istanbul, Turkey).

The study was approved by the animal local Ethics Committee (Uludağ University, HADYEK Date: 08.05.2013. Number: B.30.2.ULU.0.82.00.00/59).

Statistical analyses were performed using SPSS software version 13.0 for Windows (SPSS, Inc., Chicago, Illinois, USA). The one-way ANOVA and Duncan tests were used to compare the values. Data were shown as mean  $\pm$  standard deviation. P values <0.05 were considered significant.

## RESULTS AND DISCUSSION

While the levels of ceruloplasmin increased after 6<sup>th</sup> day, and then decreased in subcutaneous and pour-on groups ( $P < 0.001$ ). TAS levels increased up to 3<sup>rd</sup> day and then decreased following days ( $P < 0.05$ ). Total protein levels increased in the subcutaneous group until the 3<sup>rd</sup> day and then decreased, on the contrary, the increase continued until the 12<sup>th</sup> day in the pour-on group ( $P < 0.01$ ). DNA fragmentation, creatinine, AST and GGT levels slightly increased after application of subcutaneous and pour-on eprinomectin. Sialic acid level decrease after the applications but there was no statistical significance ( $P > 0.05$ ). It was concluded that eprinomectin cause a decrease in acute phase protein levels (ceruloplasmin and sialic acid), an increase apoptosis level but there was no statistical significance, also increase antioxidant capacity ( $P < 0.05$ ) and total protein levels ( $P < 0.01$ ). No significant changes were observed in AST, ALT, GGT activity and urea levels (Table 1).

The main objective of the present study was to investigate effects of eprinomectin following subcutaneous and pour on administration on apoptosis, acute phase

response, total antioxidant status, total protein, creatinine, urea levels and AST, ALT and GGT activities in cattle, not aimed to investigate antiparasitic effects or side effects.

Chlorpyrifos and dichlorvos have been proved to give rise to caspase dependent apoptosis associated to oxidative stress (Nakadai *et al.*, 2006).

Oxidants can lead to programmed cell death, avermectins caused ultrastructure changes with apoptotic characters and increased the expression of caspase-3, 8 and fas mRNA. In addition, avermectins inhibited the activities of antioxidant enzymes and augmented the MDA (malondialdehyde) content, with concentration-dependent properties in pigeon liver and reported that oxidative stress plays a role in avermectins-mediated apoptosis in pigeon liver (Yarsan *et al.*, 2003). Avermectins caused the induction of oxidative stress, because of SOD and GSH-Px activities decreased. Oxidative DNA damage cause a loss of important genetic material and apoptosis (Jin *et al.*, 2010).

Acute phase proteins and sialic acid have important role in diagnosis of inflammatory diseases determination of prognosis and detection of treatment principles (Azab and Abdel-Maksoud, 1999; Meglia *et al.*, 2001; Wang and Wu, 2017). It was reported that avermectins had some effects such as inhibition of combined drug resistance, anti-inflammatory, anti-carcinogenic and apoptosis induction (Ci *et al.*, 2009; Eckarsall, 2000; Hammond *et al.*, 2007; Kaymaz *et al.*, 1999; Yamamoto *et al.*, 1993).

Stress in cows induces acute phase proteins in blood. Ceruloplasmin has more than one function and is evaluated as acute phase protein in cows. Besides, it has an antioxidant effect by cleaning free radical in serum and tissues (Aouffen *et al.*, 2004; Arthington *et al.*, 2003). When cows are exposed to various stress factors, ceruloplasmin levels increased with the intensity of stress. However, treatment with vitamin and mineral serum ceruloplasmin levels decline due to the alleviation of stress (Arslan *et al.*, 2008). In the treatment with avermectins, it was determined that apoptosis was raised depending on increase of plasma nitric oxide level (Atakisi *et al.*, 2009). Ceruloplasmin is acute phase protein which concentration change due to different kinds of tissue damage and therefore have been identified as the biomarker of choice for diagnostic and prognostic purposes in veterinary medicine.

Sialic acid has a role as an indicator of acute phase protein (Taylor, 2001; Keleş *et al.*, 2000). It was determined that oxidative stress was increased and antioxidant activity was decreased in the rabbits infected with parasite such as *Psoroptes cuniculi*. After treatment with doramectin in the ivermectin group antioxidant activity increased and oxidative stress decreased (Kanbur *et al.*, 2008).

It was reported that period in the elevation of acute phase proteins varies. Ceruloplasmin as a basic copper carrier protein synthesized by liver cells in response to tissue damage and inflammation. Because of ceruloplasmin is a positive acute phase protein that contains sialic acid residues at the terminal position of the oligosaccharide

**Table 1:** DNA fragmentation, sialic acid, ceruloplasmin, TAS levels and some biochemical parameters in control and eprinomectin administrated groups.

Parameters	Subcutaneous					Pour-On					P	
	Control	36 <sup>th</sup> hour	3 <sup>rd</sup> day	6 <sup>th</sup> day	12 <sup>th</sup> day	20 <sup>th</sup> day	Control	36 <sup>th</sup> hour	3 <sup>rd</sup> day	6 <sup>th</sup> day		12 <sup>th</sup> day
<b>DNA</b>												
fragmentation (U=absorbance)	0.049 ±0.002	0.061 ±0.004	0.056 ±0.002	0.063 ±0.005	0.065 ±0.004	0.071 ±0.005	0.051 ±0.003	0.059 ±0.008	0.072 ±0.011	0.061 ±0.006	0.054 ±0.001	0.054 ±0.002
Sialic acid (µg/mL)	2109.60 ±136.43	2005.50 ±207.50	2050.55 ±150.22	2006.60 ±255.99	1901.75 ±258.47	1785.50 ±204.16	2029.00 ±145.27	1995.50 ±115.93	2087.40 ±198.27	1907.66 ±391.97	1813.75 ±69.97	1746.33 ±110.68
Ceruloplasmin (mg/dL)	15.79 ±2.19 <sup>a</sup>	13.55 ±1.32 <sup>ab</sup>	6.38 ±0.93 <sup>c</sup>	5.99 ±0.36 <sup>c</sup>	6.59 ±0.81 <sup>c</sup>	8.37 ±1.12 <sup>c</sup>	12.07 ±1.09 <sup>b</sup>	8.50 ±1.12 <sup>c</sup>	5.75 ±0.52 <sup>c</sup>	5.15 ±1.19 <sup>c</sup>	5.30 ±0.95 <sup>c</sup>	5.89 ±0.59 <sup>c</sup>
TAS (mmol trolox Equiv./L)	0.568 ±0.027 <sup>bc</sup>	0.570 ±0.027 <sup>bc</sup>	0.656 ±0.036 <sup>ab</sup>	0.568 ±0.028 <sup>bc</sup>	0.550 ±0.012 <sup>c</sup>	0.553 ±0.037 <sup>c</sup>	0.564 ±0.036 <sup>bc</sup>	0.572 ±0.018 <sup>bc</sup>	0.676 ±0.026 <sup>a</sup>	0.620 ±0.016 <sup>abc</sup>	0.610 ±0.035 <sup>abc</sup>	0.617 ±0.039 <sup>abc</sup>
Total protein (g/dl)	7.65 ±0.180 <sup>d</sup>	7.67 ±0.210 <sup>d</sup>	9.05 ±0.387 <sup>ab</sup>	8.15 ±0.505 <sup>bcd</sup>	8.17 ±0.70 <sup>bcd</sup>	8.99 ±0.377 <sup>abc</sup>	7.96 ±0.222 <sup>cd</sup>	8.21 ±0.186 <sup>bcd</sup>	8.85 ±0.479 <sup>abc</sup>	8.95 ±0.268 <sup>abc</sup>	9.30 ±0.185 <sup>a</sup>	8.90 ±0.238 <sup>abc</sup>
Creatinine (mg/dl)	0.944 ±0.098	0.962 ±0.078	0.924 ±0.094	1.014 ±0.105	0.934 ±0.043	0.952 ±0.063	0.848 ±0.089	0.878 ±0.067	0.894 ±0.048	0.880 ±0.098	0.987 ±0.131	1.017 ±0.098
AST (U/L)	99.00 ±21.97	103.40 ±24.69	118.80 ±25.49	87.80 ±12.95	90.80 ±14.66	87.75 ±9.80	78.00 ±7.51	91.00 ±17.50	104.60 ±25.74	73.00 ±3.74	79.00 ±4.67	75.50 ±12.73
ALT (U/L)	30.20 ±4.54	26.60 ±2.27	30.00 ±3.27	24.80 ±1.46	23.60 ±2.65	21.60 ±2.69	26.20 ±3.05	27.20 ±1.93	27.60 ±0.50	24.75 ±1.79	25.25 ±2.65	26.75 ±1.65
Urea (mg/dl)	35.80 ±4.75	30.60 ±5.51	36.20 ±5.13	36.20 ±7.39	28.40 ±2.40	41.20 ±5.09	39.80 ±2.05	30.20 ±1.65	38.60 ±1.20	35.75 ±4.30	33.00 ±2.68	39.50 ±2.72
GGT (U/L)	30.20 ±3.54	30.40 ±3.05	36.80 ±3.40	34.60 ±3.78	33.20 ±2.35	34.75 ±2.95	29.20 ±1.59	30.60 ±1.72	33.60 ±2.46	32.00 ±2.08	30.75 ±0.94	29.00 ±2.61

\*P<0.05: statistically significant, \*\*P<0.01: statistically significant, \*\*\*P<0.001: statistically significant.  
a, b, c, d: Between groups with different letters in the same row mean difference is significant.

chain, increase of ceruloplasmin level can cause an increase of sialic acid level. (Gökmen *et al.*, 2004; Güngör *et al.*, 2004; Haris, 1991; Weissman *et al.*, 1966).

Free radicals lead to damage in cells, tissues or organ by altering the structure of some biomolecules. Malondialdehyde (MDA) is the final product of lipid peroxidation from these biomolecules. Avermectins inhibit the activity of antioxidant enzymes and increase MDA content (Gameel, 1982; Zhu *et al.*, 2013; Kaymaz *et al.*, 1999; Dede *et al.*, 2000).

Eprinomectin and Ivermectin groups were compared with the control group; following a transient decrease in GSH level, it caused a temporary increase. However, there was no change in MDA levels (Bilgili *et al.*, 2009). In our study, it was determined that the total antioxidant activity increased slightly but after a certain time it was almost the same level.

Blood parameters in infected animals have a diversity compared to normal physiological values (Aksakal and Özer, 1987; Değer *et al.*, 1997). It could be due to the low antioxidant activities in infected animals. Peroxydation of membrane lipids by increased amount of free oxygen radicals in infected animals can induce tissue damage. Similar to these statement an increase of antioxidant activity was observed in the treatment group.

Protein losses in infestation with gastrointestinal helminths induce hypoproteinemia (El Gohari *et al.*, 1984; Kaymaz *et al.*, 1999; Soulsby, 1982). Plasma urea and creatin levels are commonly used parameters to determine the glomerular function. Urea concentration in blood can show fluctuations of depending on amino acids quantity and diversity taken by ration and tissue catabolism. Creatin concentration is unsusceptible to nutrition and daily synthesis is stable. Creatin passes into the bloodstream as a final product of hydrolysis of creatine phosphate in muscles (Kozan *et al.*, 2010).

AST and ALT are widely used in the increase of liver membrane permeability and GGT is used in the determination of bile duct damage. Studies have shown that the absence of major changes in the level of these enzymes during treatment has no acute effect on organs such as liver and kidney (Kozan *et al.*, 2010; Yarsan *et al.*, 2003).

The results of the study indicated that eprinomectin administration decreased levels of acute phase proteins (ceruloplasmin and sialic acid) in cows and a non-statistical increase in apoptosis level. In addition, it was determined that the increase in antioxidant capacity ( $P < 0.05$ ) and total protein ( $P < 0.01$ ) levels were statistically significant. Non statistically changes in AST, ALT, GGT, urea and creatinine levels showed that eprinomectin had no adverse effects on liver and kidney.

## CONCLUSION

Treatment with anthelmintic drugs increase the antioxidant capacity. So it alleviates oxidative damage and this can reduce plasma acute phase protein concentrations. In conclusion, ceruloplasmin and sialic acid values can be

important indicator of early diagnosis, treatment and preventive protection on both infectious and noninfectious diseases. These findings indicate that it might be used as auxiliary laboratory analysis to follow up the effects of avermectins and parasiter diseases.

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