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Evaluation of the Effect of Buparvaquone Used in the Treatment of Neonatal Calves Naturally Infected with *Cryptosporidium Spp.* on Renal and Hepatic Functions

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Abstract

Cryptosporidium parvum is a zoonotic protozoan that causes neonatal calf diarrhea common in the world. Buparvaquone, which is known to have very positive effects on oocysts, which are the main reserve in the spread of infection, has not yet been investigated for its hemato-biochemical aspect in calves with cryptosporidiosis. In the present study, the effect of buparvaquone on renal and hepatic functions in naturally infected newborn calves with cryptosporidiosis was investigated. A group was formed for this study using only a total of ten calves (n=10) naturally infected with cryptosporidiosis. Buparvaquone 2.5 mg/kg intramuscular injection was administered as a single dose to all calves in the group. Laboratory analyses and statistical calculations of blood and serum samples taken on the specified days were made. According to the results we obtained in the study, it was observed that the renal and hepatic effects of the drug after a single dose injection of buparvaquone to calves with neonatal cryptosporidiosis remained within normal limits, similar to the methods safely applied in the treatment of cryptosporidiosis in the field.

Keywords: Cryptosporidiosis, calves, renal, hepatic, buparvaquone

Introduction

Cryptosporidium Spp. is a protozoan of zoonotic importance that causes diarrhea and some gastrointestinal clinical findings in humans, domestic and wild animals.[1] Cryptosporidiosis, usually caused by *Cryptosporidium parvum*, is one of the leading causes of waterborne diarrheal epidemics worldwide.[2] Fecal-oral;[3] The agent, which is transmitted through contaminated feed, water and contact with infected calves;[2,4] brings with it important environmental problems.[5,6,7] It is an important problem in cattle breeding, as it suppresses the immune system in newborn and young calves, causing severe diarrhea and heavy losses such as death due to dehydration.[8,9] Clinical symptoms observed in infected calves can range from asymptomatic to collapse and death.[9,10,11,12] The infection is usually acute watery diarrhea, depression, weakness, loss of appetite in calves;[13] diarrhea and weight loss, depression are observed in small cattle.[8,14] Since C.*parvum* adheres to the apical part of enterocytes in the intestines and causes villous atrophy,[15] there is a strong association between growth retardation[16,17] and persistent diarrhea, especially in chronic infections. It has been stated that there is a relationship.[18]

Due to the ease with which samples can be analyzed automatically, the use of biochemical and hematological measurements is increasing day by day as an aid in the diagnosis of infections or the determination of the metabolic profile.[19] Diagnosis can be made by comparing the reference values of the healthy population with clinical cases (Knowles 2000; Mohri et al. 2007).[19,20] Reference values are available for each animal species for appropriate interpretation of biochemical and hematological results, and these tests are widely used in the veterinary health field to aid in

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the diagnosis of diseases.[20]

Buparvaquone is an antiprotozoal drug belonging to the hydroxynaphthoquinone group, similar to parvaquone and atovaquone, and is still considered the only effective therapeutic agent in the treatment of tropical theileriosis caused by *Theileria annulata*.[21,22] It has been reported that the efficacy of buparvaquone, which is used in the treatment of neonatal calves naturally infected with cryptosporidiosis, on oocyst scattering is quite successful.[23,24] In the literature review, it was determined that the hemato-biochemical effects of the drug in calves with cryptosporidiosis were not investigated.

The aim of this study is to determine the hemato-biochemical changes after a single dose of buparvaquone administration in neonatal calves naturally infected with cryptosporidiosis and to contribute to improving the treatment of the disease.

Materials and Methods

The material of the study consisted of 20 Holstein calves with the same care and feeding conditions in XXX Animal Health Research and Application Center. The first day when diarrhea was observed in calves was accepted as day 0, and only calves with positive C.*parvum* results from the rapid test kit were included in the study. The study group was formed with 10 calves with similar gender and age distribution (6-8 days old). A single dose of buparvaquone (Butalex-MSD® Germany) 2.5 mg/kg/im was applied to the neck muscles of all calves in the group.[12] Separate sterile injectors were used for each calf. 5 ml blood samples were taken from the jugular veins of the calves on the first day, the third day and the seventh day of the treatment, when diarrhea was observed before the treatment, using sterile vacutainer needles in one dry tube with and without anticoagulant following the rules of asepsis and antisepsis.

The serums obtained as a result of keeping the blood in the tubes without anticoagulant in a centrifuge device (NF200, Nüve, Türkiye) for 5 minutes at 3000 rpm without wasting time were transferred to eppendorf tubes (2 ml, Biosigma, Italy) and YYY University Veterinary Faculty Internal Diseases Department Central It was stored at -20 °C in the deep freezer in Laboratory-2. Hemogram analyses of blood samples taken into EDTA tubes were performed at Bursa Uludag University Veterinary Faculty Internal Medicine Central Laboratory-1 (Abaxis Vetscan HM5, veterinary hematology analyzer, Hungary). Biochemical parameters such as AST (Aspartate Aminotransferase), GGT (Gamma Glutamyl Transferase), TP (Total Protein), ALB (Albumin), urea, CRE (Creatinine) were evaluated from serum samples (Mindray perfect plus, WD-86100002T, Shenzhen, P.R. China).

Statistical Analysis

Statistical evaluations were made with SPSS v22 and MedCalc V19 programs. In the statistical analyses of the results obtained from the findings, the Shapiro-Wilk method was applied in the normality tests of the data. Descriptive statistical results of the data were given as mean ± SE for normally distributed data, and as median (min-max) for non-normally distributed data. The "One Way Repeated Measures ANOVA" test was used for repeated measurements within the group. Tukey or Holm-Sidak method was used as Post-Hoc test to determine the statistical difference between different days in repeated measurements. The non-parametric test Freidman's method was used for the data that were not normally distributed. This study was carried out with the approval number 2021-01/04 by ZZZ University Animal Experiments Local Ethics Committee (HADYEK).

Results and Discussion

Although the mechanism of action of atovaquone, which is in the antiprotozoal hydroxy naphthoquinone group, has not been fully determined, it has been stated that the parasite inhibits mitochondrial electron transport and causes collapse of the mitochondrial membrane by acting on the cytochrome b gene on the mitochondrial inner membrane.[25,26] It is thought that buparvaquone used in the treatment disrupts the mitochondria of the parasite in the early period and therefore, due to its structural similarities, buparvaquone acts similarly to atovaquone used in the treatment of *Toxoplasma gondii* and malaria.[27,28] Buparvaquone has been reported to show 100-fold increased activation against amastigotes (intracellular parasitic form) compared to other hydroxynaphthoquinones.[11,29,30] In the routine leukogram of calves infected with cryptosporidiosis, no significant change occurs without a secondary infection. However, there may be significant increases in hematocrit values depending on the degree of dehydration.[31] In the statistical evaluation of WBC (White Blood Cell), LYM (Lymphocyte), NEU (Neutrophil), and RBC (Red Blood Cell) values in hemogram results, a statistically significant decrease was found in WBC values when the pre-treatment 0th day and the third day after treatment were compared ($p<0.05$). Average WBC ($\times 10^9$ /L) concentrations categorized by days are presented in (Table 1) Total leukocyte value was found to be within the normal reference values before treatment. Significant reductions were observed, albeit within the normal reference range,

on the third and seventh day after treatment with buparvaquone. In the study conducted by Neamet-Allah (2016), it was observed that there were decreases in WBC, LYM, and NEU levels after treatment with buparvaquone compared to before treatment. Similar findings were obtained in our study.[32] These changes are probably related to the activity of buparvaquone on oocysts and the suppression of inflammatory mediators.[24] There was a statistically significant increase in LYM ($\times10^9$ /L) values between the 3rd, and 7th day after treatment ($p<0.05$) (Table 1). Considering the NEU ($\times10^9$ /L) values, a statistically significant increase was determined between the 0th and 3rd days of comparison ($p<0.005$) (Table 1). Likewise, the increase in the evaluation between the 0th and 7th days was statistically significant ($p<0.001$) (Table 1). No statistical significance was found in intragroup measurements in the number of RBC (×1012/L) ($p>0.05$) (Table 1).

Table 1. Statistical differences in mean WBC, LYM, NEU, RBC, HGB, HCT, PLT values at 0th, 3rd, and 7th days

	0th Day	3rd Day	7th Day
WBC ($\times10^9$ /L)	6,98±^{a} 0,88	5,54±^{b} 2,15	6,06± 2,07
LYM ($\times10^9$ /L)	1,98 (0,84-5,10)	1,65±^{a**} 0,34	2,63±^{b**} 0,47
NEU ($\times10^9$ /L)	4,21±^{a} 0,45	2,87±^{b***} 0,58	2,25±^{c***} 0,32
RBC ($\times10^{12}$/L)	7,67± 0,47	7,67± 0,37	7,64± 0,49
HGB (g/L)	9,26±^{a**} 0,67	8,82±^{b**} 0,55	8,44±^{bcx} 0,64
HCT (L/L)	27,46±^{axx} 2,16	25,77±^{b} 1,74	25,03±^{bcx} 1,91
PLT ($\times10^9$ /L)	873,10±^{a} 117,30	648,10±^{b} 62,53	666,80±^{b} 76,48

For statistical differences within the group; different letters represent statistical differences. There is no statistical difference between the measurements that do not contain any letters.*p<0.01, **p<0.05, ***p<0.001, x: p=0.001.

Considering the hemoglobin (HGB) (g/L), hematocrit (HCT) (L/L), and platelet (PLT) ($\times10^9$ /L) values; Decreases in HGB values between 0th and 3rd days ($p<0.05$) and 0th-7th days were found to be statistically significant ($p=0.001$) (Table 1). Similar decreases in HGB values were observed in studies after buparvaquone administration.[32] In the presented study, although the HCT and HGB values were within the normal reference values in both groups before treatment,[33] although the decreases in HCT values continued on the 0th, 3rd, and 7th days, on the 0th-3rd day ($p<0.05$) and While the decreases between the 0th and 7th days were found to be statistically significant ($p<0.01$), no statistical significance was found in the HCT value between the third and the seventh day (Table 1). Significant decreases in HCT compared to pretreatment may be associated with reduced gastrointestinal fluid loss. It has been reported that erythropenia, leukopenia, and low hemoglobin can be observed in the blood of calves with cryptosporidiosis, and it has been stated that this may be due to the changes that lead to destruction in the hematopoietic organs with the decrease in the oxygen level in the blood.[34] It was determined that the decrease in the mean values was statistically significant in the comparison of PLT values before and after treatment at 0 and 3 days ($p<0.05$). The platelet count in calves in the first three days of their life is around 400×10^9 /L. It can reach 900×10^9/L by showing a rapid increase on the tenth day. In a study conducted in Norway, the platelet count was observed to be 987×10^9/L in 2-week-old calves, and it was reported to be 518×10^9/L after the third week.[35]

AST, GGT, urea, Cre, TP, and ALB levels were measured to evaluate the effect of buparvaquone on liver and kidney functions in calves on day 0 before treatment and on days 3 and 7 after treatment. Many publications were considered for the reference range for calves in biochemical evaluation.[32,33,37,38] AST, GGT, urea, Cre, TP, and ALB were not statistically significant in the results obtained (Table 2). TP concentration may be lower in neonatal calves than in adult cattle.[39] Although it rises rapidly following ingestion of colostrum, it is still low compared to adults. In the presented study, TP concentration was determined to be within the normal reference values before treatment. Although there is no statistical significance, it was determined that the TP concentration was higher before the treatment. It is thought that the decrease in the TP concentration occurs with the disappearance of the dehydration findings as a result of the improvement in the stool score after the treatment. Similar changes were observed in ALB concentration. In the analyses performed, ALB was not found to be statistically significant at 0, 3, and 7 days ($p>0.05$) (Table 2). Similar results were obtained in a study conducted with halofuginone, which is in the same group as buparvaquone.[40] When the Cre concentration is examined, it is seen that the decrease on the 7th day after the treatment compared to the pre-treatment is statistically significant ($p<0.05$) (Table 2).

Table 2. Statistical differences in mean TP, ALB, CRE, AST, GGT, Urea values at 0th, 3rd, and 7th days

	0th Day	3rd Day	7th Day
TP (g/dl)	6,71±^{a*}0,32	6,32±^{b*}0,33	6,29±0,35
ALB (g/dl)	2,56±0,59	2,57±0,48	2,58±0,42
CRE (mg/dl)	0,29±^{a*}0,02	0,26±0,01	0,23±^{b*}0,01
AST (U/L)	27,70±^{a*}3,96	36,10±1,84	45,60^{b*}27-93
GGT (U/L)	268,30±^{a***}42,48	169,90±^{b**}22,82	109,90±^{c**}13,71
Urea (mg/dl)	47,60±^{a*}3,97	42,32±^{b*}3,03	31,91±^{c*}3,08

Different letters represent statistical difference. $^*p < 0,05$ $^{**}p < 0,005$ $^{***}p\leq0.001$

AST (U/l) level 0-7. A statistically significant increase was determined between days ($p<0.05$) (Table 2). Although it was within the normal reference values, a significant increase was found in the AST evaluation on days 0-7 in calves after treatment ($p<0.05$) (Table 2). It is thought that

this increase may result from a partial muscle injury following the intramuscular injection of buparvaquone or from the negative effects of buparvaquone on liver functions.[41] It is thought that this may be due to the fact that buparvaquone suppresses the inflammatory processes occurring in the intestines and limits the fluid-electrolyte balance losses. However, there are not enough studies on this subject, there is a need for new research on the subject. Decreases in GGT (U/l) levels on the 0th and 3rd days before the treatment and the 3rd, and 7th days after the treatment are remarkable ($p \leq 0.001$) (Table 2). GGT is an indicator of early passive transfer, and GGT enzyme activation can increase up to 5000 IU/L following a sufficient amount of colostrum intake.[42] It has been reported that this value decreased in the following days. Although the calves included in the study were at an average age of 7 days, high GGT activities may indicate that the calves received sufficient colostrum after birth. The decrease in GGT concentration on the third and seventh days after treatment compared to pre-treatment is thought to be due to time-dependent decreases in maternal antibodies taken with colostrum.

The formation of urea (mg/dl) is related to the hepatic metabolism of ammonia, and most of the ammonia in the blood is produced in the intestines and absorbed and is included in the portal circulation, and the liver converts ammonia to urea and is thus removed from the body.[43,44] The urea concentration may increase in calves with diarrhea in relation to dehydration, and the resulting glomerular filtration may directly cause renal failure in calves with ongoing severe diarrhea. In the presented study, it can be accepted that the urea concentration before treatment is higher than the urea concentration values specified in one-week-old calves.[45] It is thought that the disappearance of the signs of partial dehydration due to the positive progress of the stool score after the treatment, causing the urea concentration to decrease significantly on the third and seventh days.

In a study conducted in Neamet-Allah 2016, it was reported that hematological and biochemical values returned to the normal reference range two weeks after the administration of buparvaquone.[32]

Conclusion

In conclusion, the fact that the hemogram and biochemical parameter values of the calves administered buparvaquone remained within the normal reference limits and no statistically significant change was observed in the present study provides data that removes the doubts about the reliability of buparvaquone in terms of renal and hepatic effects. In addition, it was concluded that buparvaquone did not cause problems in organ functions and inflammatory processes, with this study, which was performed for the first time in calves with cryptosporidiosis, while hemato-biochemical parameters remained at reference values.

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