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Effect of *Mannheimia (Pasteurella) haemolytica* Infection on Acute-phase Proteins and Some Mineral Levels in Colostrum–Breast Milk-fed or Colostrum–Breast Milk-deprived Sheep

P. A. Ulutas[1,*] and A. Ozpinar[2]
[1]*Adnan Menderes University, Faculty of Veterinary Medicine, Department of Biochemistry, Isıklı, Aydın;* [2]*Istanbul University, Faculty of Veterinary Medicine, Department of Biochemistry, Istanbul, Turkey*
[*]*Correspondence: E-mail: paulutas@adu.edu.tr*

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ABSTRACT

The aim of this study was to investigate the levels of acute-phase proteins and minerals as indicators for the reactivity in 1-year-old sheep. A total of 26 Chios breed sheep were fed colostrum–breast milk (control, $n = 15$) or were deprived after separation from their mother immediately after birth (experimental, $n = 11$). *Mannheimia (Pasteurella) haemolytica* serotype A1 was inoculated intratracheally and blood samples were taken in vacuumed sera on days 0, 1, 4, 7, 10, 13, 16, 19 and 22. Antibiotic treatment was initiated after blood sampling on day 22, and blood samples were taken on days 1, 4 and 7 after the treatment. The levels of C-reactive protein (CRP), haptoglobin, ceruloplasmin, fibrinogen, zinc, iron and calcium, which are the indicators of immune function and infectious diseases were analysed. No significant difference between the control and trial groups before and after the infection was determined. However, serum CRP, haptoglobin, ceruloplasmin and fibrinogen levels were increased in the course of the infection. These levels were restored to normal following treatment.

Keywords: acute-phase proteins, zinc, iron, colostrum, *Mannheimia (Pasteurella) haemolytica*, sheep

Abbreviations: APP, acute-phase proteins; CRP, C-reactive protein; IL, interleukin; PMSG, pregnant mare serum gonadotrophin; TNF, tumor necrosis factor

INTRODUCTION

The acute-phase response is the reaction of the animal to disturbances in its homeostasis caused by infection, tissue injury, neoplastic growth or immunological disorders. It is characterized by alterations in the concentrations of a variety of hepatocyte-derived acute-phase proteins (APPS) in the blood, fever and endocrinological, metabolic, immunological and neurological changes (Pfeffer *et al.*, 1993). Many of these changes have been shown to be induced by cytokines including IL-1, IL-6 and TNF-α (Gruys *et al.*, 1994; Van Miert, 1995). The acute-phase response is thought to be beneficial for the injured animal in acting to restore homeostasis and prevent microbial growth (Gruys *et al.*, 1994). Measurements of acute-phase proteins during infectious or inflammatory conditions are useful for diagnosis, prognosis and assessing the response to treatment (Kent, 1992; Gruys *et al.*, 1994; Eckersall, 2000; Ganheim *et al.*, 2003).

Haptoglobin is considered to be the main APP in cattle and has been reported to be a useful indicator of bovine bacterial infections (Eckersall, 2000). Haptoglobin is not or is hardly detectable in healthy animals but increases significantly after infection or inflammation (Conner *et al.*, 1989; Skinner *et al.*, 1991; Pfeffer *et al.*, 1993; Wittum *et al.*, 1996; Horadogada *et al.*, 1999). Ceruloplasmin is thought to function as an antioxidant, protecting endothelial cells from oxidative injury during inflammation (Deignan *et al.*, 2000). In humans, dogs, pigs and horses, C-reactive protein (CRP) is a major APP, displaying a rapid and pronounced rise in its serum concentration in response to infection or tissue injury (Caspi *et al.*, 1987; Yamashita *et al.*, 1991; Yamamato *et al.*, 1993; Clayes *et al.*, 2002). It has been reported that fibrinogen concentration increases during acute-phase reactions (Conner *et al.,* 1989; Tamzali *et al.*, 2001; Ganheim *et al.*, 2003).

In some experimental or natural bacterial and viral infections or administration of inflammatory agents and endotoxins, the rise in body temperature is accompanied by low iron and zinc levels, induced by some pyrogenic and metabolic reactions. The clinical importance of alterations of these trace elements in serum is their use as indicators of infection and the decline in mortality and morbidity when they are administered exogenously (Van Miert, 1995; Voyvoda *et al.*, 1997). Calcium has several important functions in formation of bone and dental tissues, in the release of hormones, in contraction of muscles and in glycogen metabolism (Dai *et al.*, 1992).

Mannheimia infection is characterized by clinical symptoms of pleuritis and pneumonitis such as fever, asphyxia, depression and pathological symptoms (Ackerman and Brodgen, 2000). *Manheimia (Pasteurella) haemolytica* infection causes significant economic losses in cows, goats and sheep such as body weight loss, medical treatment expenses and death (Kimberling, 1988; Brennan *et al.*, 1998).

Colostrum is the early milk produced during the first several post-parturition days. This early milk has a nutrient profile and immunological composition that differs substantially from mature milk. In addition to macronutrients found in milk such as protein, carbonhydrate and fat, and micronutrients including vitamins and minerals, colostrum contains oligosaccharides, growth factors, antimicrobial compounds and immune-regulating constituents (Pattison *et al.*, 1995; O'Doherty and Crosby, 1997; Uruapka *et al*., 2002; Kelly, 2003). Deprivation of colostrum in animals in early life causes hypoimmune activity, low body weight, high mortality and high infection prevalence (Lamotte, 1977; Arthington *et al.*, 2000). In addition, passive immune status at postpartum hour 24 was an important determinant of long-term health and performance (Wittum *et al*., 1996). It has been reported in several human studies that colostrum deprivation after birth, may be related to various diseases in adulthood (Saarinen and Kajosaari, 1995; Gdalevich *et al.*, 2001; Sears *et al.*, 2002). However, no reports were found demonstrating that diseases occurring at adulthood were related to postpartum feeding in animals. In one study, Wittum and colleagues (1996) reported that passive immunity is an important marker of the health status and performance of calves before and after weaning. The aim of this study was to investigate the levels of acute-phase proteins and some minerals used as indicators of reactivity in adult sheep that have been colostrum–breast milk fed or deprived after birth, to determine the importance of these tests in monitoring the pathogenesis, prognosis and the course of the treatment in infectious diseases encountered in adulthood.

MATERIAL AND METHODS

Animals

Twenty Chios ewes (3–4 years old) were purchased from Istanbul University Faculty of Veterinary Medicine Research Farms. Intravaginal sponges were used for oestrus synchronization in the ewes (Senkron Sponge, Vetifarm, 60 mg medroxyprogesterone acetate). Fourteen days after sponge application, PMSG (Syncroject 600/6000 PMSG) was injected at a dose of 500–750 IU/ewe. The ewes were mated with Chios rams. After parturition, one lamb of each pair twins was kept with the ewe (control group, $n = 15$) and other was removed immediately after birth and housed in isolated boxes (experimental group, $n = 15$). After parturition, the lambs in the experimental group were fed with commercial cow is milk via bottle feeding *ad libitum* and then milk replacer was given ad libitum for 6 weeks. Lambs in the control group were fed colostrum and mother's milk for 6 weeks. Four of the 15 experimental lambs died from different causes such as enteritis and pneumonia. After 6 weeks, lambs in both groups were fed with concentrated food, dried grass and water *ad libitum* until 1 year of age.

Clinically healthy, helminth-free sheep fed with or without colostrum and mother's milk (control, $n = 15$; experimental, $n = 11$) after birth were used. Body weight of the sheep was estimated before the *Mannheimia haemolytica* inoculation.

Sample collection and analysis

Mannheimia (Pasteurella) haemolytica serotype A1 (103426 ATCC) strain (1×10^9) was administrated to lambs of both groups by the intratracheal route. Blood samples were collected via jugular venepuncture into serum and plasma tubes on days 0, 1, 4, 7, 10, 13, 16, 19 and 22 following inoculation. On the day 22, an antibiotic treatment was initiated after the blood sampling, blood samples were taken and on days 1, 4 and 7 of treatment. Sera and plasma samples were stored at −20°C until the day of analysis. The concentration of haptoglobin was measured by the spectrophotometric method of Skinner and colleagues (1991), which is based on the haemoglobin-binding capacity. Methaemoglobin was prepared from fresh ovine erythrocytes and diluted with water to give a working concentration of 0.278 g/L. Hydrogen peroxide (0.02 mol/L) was prepared in water; guaiacol (0.06 mol/L) was prepared in sodium acetate buffer (pH 4.0). Each analysis used 10 μl of test serum, blank and standard, incubated at 25°C with 90 μl methaemoglobin for 10 min. Guaiacol (1.5 ml) was added, immediately followed by 0.5 ml hydrogen peroxide to all tubes at timed intervals. The tubes were kept at 25°C for 8 min before the absorbance was read at 470 nm. The blank used was serum from clinically normal sheep with no detectable haptoglobin. Human haptoglobin was used as the standard. Plasma ceruloplasmin level was measured as described by Colombo and Richterich (1964). Serum CRP, Fe and Ca levels were measured by autoanalyser (Merck Vitalab Selectra 2) using commercially available kits (Diasis Diagnostic, Germany). Plasma fibrinogen levels were determined by a heat precipitation method as described by Millar and colleagues (1971). The serum was diluted 20:1 with a solution of 0.1 mol/L HCl and then analysed for Zn by means of an atomic absorption spectrophotometer (Variant Spectra AA 220) as described previously (Camas *et al.*, 1999).

Student's *t*-test was used to test for significance of differences between groups and analysis of variance was used to determine between blood sampling days.

RESULTS

Mean body weight of the controls (31.09 ± 1.81 kg) was significantly ($p < 0.05$) higher than in the experiment group (24.93 ± 1.63 kg). Signs of depression were observed 24–72 h after challenge in both groups. Dry cough was developed in some lambs and others had a rough coat and nasal discharge. These signs remained until treatment in control and trial groups. At the end of the treatment, no clinical signs were noted in any of the lambs.

The mean concentration of haptoglobin before the inoculation of bacteria was 0.16 ± 0.13 g/L in the control group and 0.19 ± 0.10 g/L in the experimental group. The peak haptoglobin levels occurred at the 10th day in the control group (1.5 ± 0.72 g/L) and at the 13th day in the experimental group (1.61 ± 0.62 g/L). These high levels decreased slowly after the 13th day of infection. After the inoculation of bacteria, the mean haptoglobin levels were significantly ($p < 0.001$) increased in both groups. There were no significant differences between the haptoglobin concentrations in the two groups (Figure 1).

The mean concentration of ceruloplasmin before the inoculation of bacteria was 11.8 ± 2.3 mg/dl in the control group and 13.5 ± 1.8 mg/dl in the experimental group, and the mean ceruloplasmin level was increased significantly ($p < 0.001$) in the two groups until the 10th day of infection. The peak ceruloplasmin levels occurred at the 7th day in control group (20.91 ± 4.0 mg/dl) and the first day in the experimental group (20.75 ± 4.0 mg/dl). These high levels were restored to normal following the treatment. There were no significant

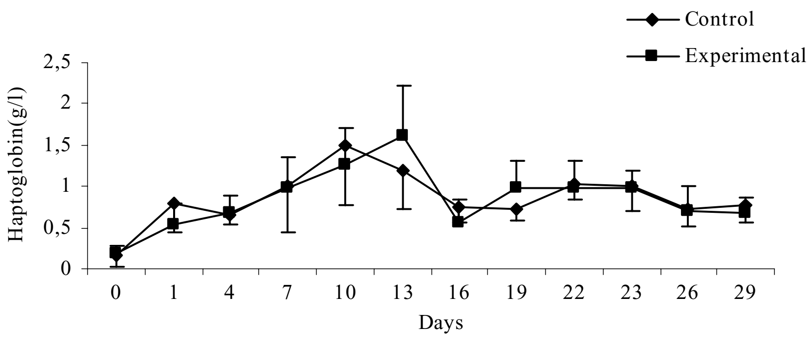

Figure 1. Mean ± SD serum haptoglobin levels after bacterial inoculation in sheep fed with colostrum (control, $n = 15$) and deprived of colostrum (experimental, $n = 11$)

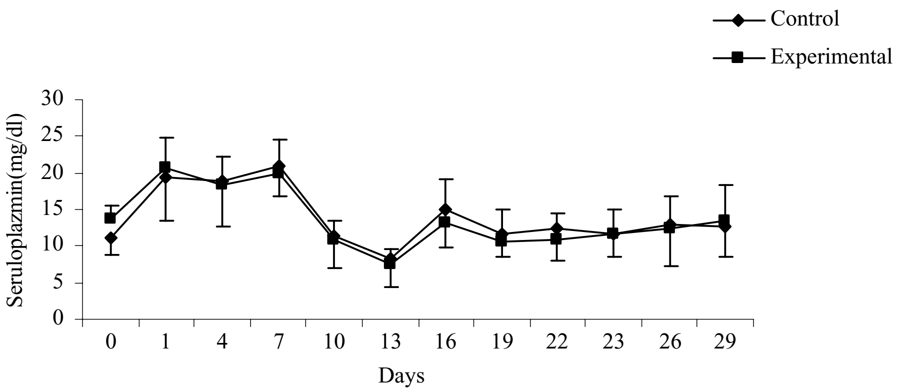

Figure 2. Mean ± SD serum ceruloplasmin levels after bacterial inoculation in sheep fed with colostrum (control, $n = 15$) and deprived of colostrum (experimental, $n = 11$)

differences between the ceruloplasmin concentrations in two groups before and after infection (Figure 2).

The mean concentration of CRP before the inoculation of bacteria was 0.51 ± 0.19 mg/dl in the control group and 0.55 ± 0.10 mg/dl in the experimental group, and the mean CRP level was significantly ($p < 0.001$) increased in both groups following bacterial inoculation. The peak CRP levels occurred at the first day in both control (0.82 ± 0.18 mg/dl) and experimental groups (0.91 ± 0.13 mg/dl). There were no significant differences between the CRP concentrations in two groups before and after infection (Figure 3).

The mean concentration of fibrinogen before the inoculation of bacteria was 436.2 ± 39.5 mg/dl in the control group and 437.5 ± 47.8 mg/dl in the experimental group. At the first day of infection, the mean fibrinogen level was increased significantly ($p < 0.001$) in both groups. The peak fibrinogen levels were 599 ± 60.37 mg/dl in the control group and

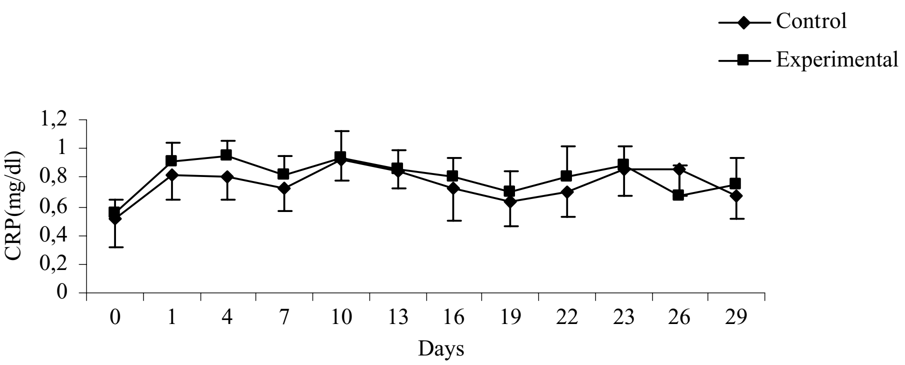

Figure 3. Mean ± SD serum levels after bacterial inoculation in sheep fed with colostrum (control, $n = 15$) and deprived of colostrum (experimental, $n = 11$)

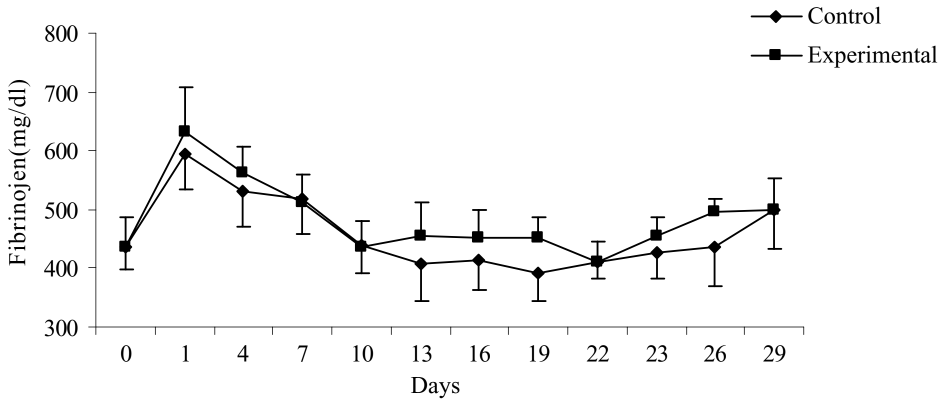

Figure 4. Mean ± SD serum fibrinogen levels after bacterial inoculation in sheep fed with colostrum (control, $n = 15$) and deprived of colostrum (experimental, $n = 11$)

633 ± 75.16 mg/dl in the experimental group at the first day. These levels were restored to normal following the treatment. There were no significant differences between the fibrinogen concentrations in two groups before and after infection (Figure 4).

The serum Fe levels on days 1, 4, 10, 13 and 16 were statistically lower ($p < 0.001$) than at day 0; no significant differences were determined between days 0 and 19 in the control group. At the beginning of the antibiotic treatment, serum Fe levels were increased, and this increase continued to the end of the treatment. In experimental group, serum iron level was decreased on days 1 and 4 of antibiotic treatment. Low Fe levels continued on other blood sampling days, but there was no statistically significance. Serum Zn levels on days 1, 4, 7 were significantly lower ($p < 0.001$) than at day 0 in the control group. Similar results were observed in the experimental group. Serum Ca level on the first day was lower ($p < 0.05$) than at day 0 in the control group. There were no significant differences in experimental group. There were no statistically significant differences between groups in serum Fe, Ca and Zn levels (Figures 5, 6 and 7).

DISCUSSION

Colostrum, a nutrient-rich fluid produced by female mammals immediately after giving birth, is loaded with immune, growth and tissue repair factors. Studies concerning the effects of colostrum have been made in postpartum period in animals (Pattison *et al.*, 1995; O'Doherty and Crosby, 1997; Uruapka, 2002). Deprivation of colostrum in animals in early life causes hypoimmune activity, low body weight, high mortality and high infection prevalence (Lamotte, 1977; Pattison *et al.*, 1995; O'Doherty and Crosby, 1997; Arthington *et al.*, 2000). Wittum and colleagues (1996) reported that passive immunity was an important marker of the health and performance in calves before and after weaning. In our study, adult sheep in the experiment group showed significantly decreased body weights compared to

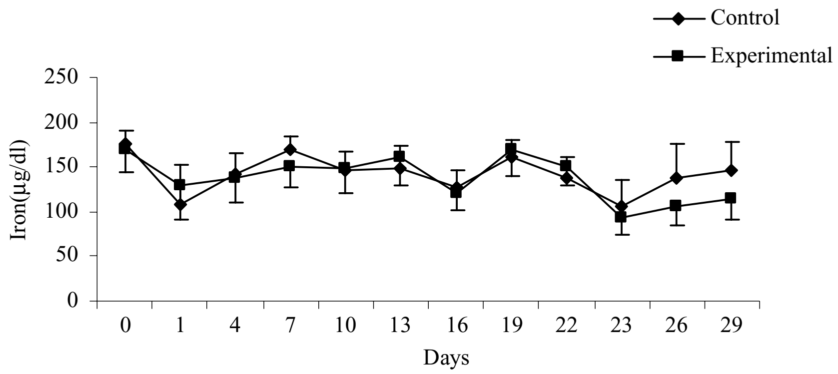

Figure 5. Mean ± SD serum Fe levels after *Pasteurella haemolytica* infection in control ($n = 15$) and experimental ($n = 11$) groups

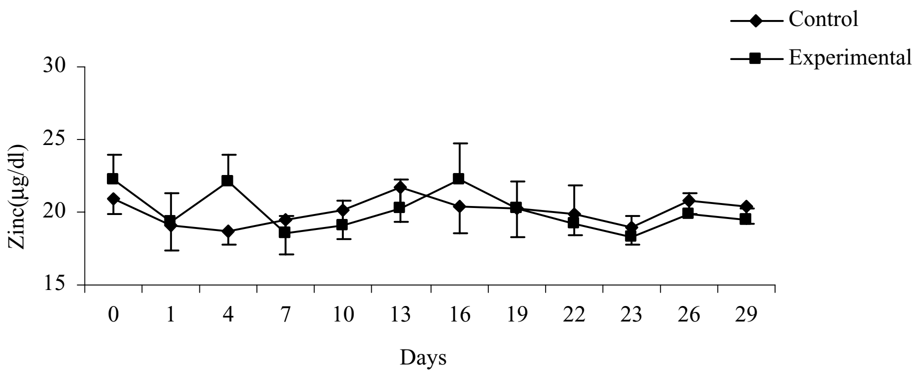

Figure 6. Mean ± SD serum Zn levels after *Pasteurella haemolytica* infection in control ($n = 15$) and experimental ($n = 11$) groups

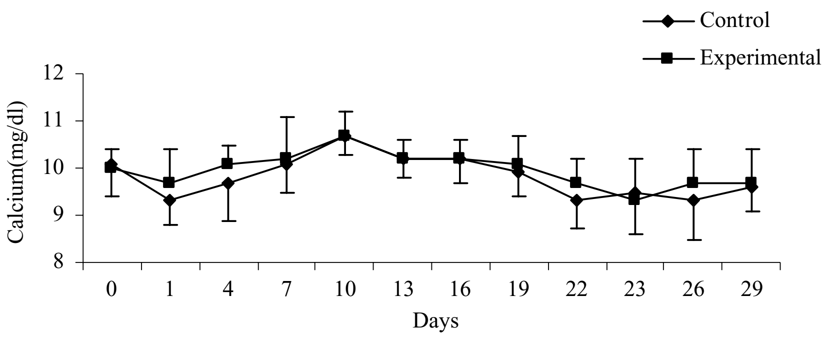

Figure 7. Mean ± SD serum Ca levels after *Pasteurella haemolytica* infection in control ($n = 15$) and experimental ($n = 11$) groups

the controls as a result of the deprivation of colostrum–breast milk after birth. Furthermore, in the experimental group, 4 of the 15 lamb died from various causes, but no deaths were seen in the controls.

Measurement of the acute-phase proteins is a potentially useful clinical tool in veterinary medicine, but further studies are required to assess their responses in different pathological processes according to the species (Kent, 1992; Gruys *et al.*, 1994). The haptoglobin, ceruloplasmin and fibrinogen concentrations have been reported to increase in many infections and inflammatory conditions in ruminants (Conner and Eckersall, 1988; Conner *et al.*, 1989; Skinner *et al.*, 1991; Pfeffer *et al.*, 1993; Wittum *et al.*, 1996; Horadogada *et al.*, 1999; Ganheim *et al.*, 2003). In our study, haptoglobin, ceruloplasmin and fibrinogen concentrations significantly increased in both groups after administration of bacteria. Serum CRP levels increase in many infections and inflammatory condition in humans, dogs, pigs and horses (Caspi *et al.*, 1987; Yamashita *et al.*, 1991; Yamamato *et al.*, 1993; Clayes *et al.*, 2002). It is not clear whether CRP is an acute-phase reactant in ruminants; however, Schrold and colleagues (1995) showed that CRP concentrations in cattle with bovine mastitis were 10 times greater than in healthy dairy cows. Similarly, Lee and colleagues (2003) reported that serum CRP levels had a correlation with the health condition of the diary herd. Vojtic and Krajne (2000) suggested that CRP was helpful in distinguishing the normal and pathological conditions in sheep. Similarly, in this study, the mean serum CRP level was significantly increased in both groups after the bacterial inoculation.

Synthesis of certain plasma proteins occurs in response to stimulation of hepatocytes by acute inflammatory response mediators. In the present study, selected acute phase proteins were monitored during infection in sheep with different feeding regimes after birth. In general, the results showed that there were similar increases in both groups. The magnitude of response was also similar. Colostrum-deprived calves after birth compared with colostrum-fed ones are reported to be more sensitive to infection in the first few months (Hodgins and Shewen, 2000). This is related to the passive immunity in this period, which depends on maternal antibodies. However, the response in subsequent infections may be identical by evading this risky period, development of the calves' immunity and institution of appropriate care and feeding conditions.

It is reported that serum iron and zinc concentrations decrease in many experimental infections of mammals and poultry. The multiplication of bacteria that require iron and zinc for growth is inhibited by lactoferrin and transferrin (Van Miert, 1991). During the acute-phase response, Fe and Zn concentrations decline substantially (Hayes, 1994). These changes reflect changes in cation binding of plasma proteins and, more importantly, alterations in cellular uptake mechanisms (Depelchin *et al.*, 1985; Hayes, 1994). In addition to fever, infected animals characteristically exhibit lower plasma Zn and Fe concentrations. This has been demonstrated in cattle suffering from *E. coli* mastitis, in veal calves with salmonellosis and pasteurellosis, in horses with *Streptococcus zooepidemicus* infections and in goats with tick-borne fever (Van Miert, 1991). In this study, after bacterial inoculation, serum Fe and Zn levels were decreased in both groups. Similarly to our results, Voyvoda and colleagues (1997) reported that serum Fe levels decreased in sheep with babesiosis and that the low Fe levels return to normal values following treatment. Smith and Cipriano (1987) reported that, serum Fe levels are 25% lower in horses with localized tissue injury than in healthy animals. Another study in horses suggested that serum Fe concentration decreased after experimental inflammatory stimulus and and that serum Zn levels were decreased significantly on day 1 and returned to normal on day 50 (Auer *et al.*, 1989). C-reactive protein, a protein that increases in plasma during acute-phase reactions, has strong protein-binding properties. It is thought that when CRP is elevated and bound to calcium in the blood, serum Ca levels decrease. However Clayes and colleagues (2002) reported no significant correlation between serum CRP, Ca and paracalcitonin levels. Decrease of serum Ca levels has been demonstrated, in septicaemic sheep and pigs (Carlsted *et al.*, 2000; Clayes *et al.*, 2002). In this study, serum Ca levels decreased following bacterial administration only on day 1 and then returned to normal values in the control group.

Body weights of the sheep in the experiment group were significantly lower than those of the controls because the colostrum–breast milk contains nutrients and growth factors, some of which are found only in colostrum. Moreover, sheep with different nutritional programmes after birth did not show significantly different responses to an induced *Mannheimia (Pasteurella) haemolytica* infection in adulthood and the responses appeared to be related to the severity of the infection and adequacy of the immune system. Additionally, it was concluded that acute-phase proteins could be used in the diagnosis and determination of the infection and monitoring of the response to therapy.

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