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Prophylactic Effects of Meloxicam in *E. coli* Endotoxin Induced Effects in Camels

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Abstract: Intravenous injection of *Escherichia coli* endotoxin at a dose of 0.1 mg kg^{-1} body weight to camels caused significant higher temperature and fever lasted initially 9 h, compared to saline treated animals. Endotoxin also caused significant increase in serum concentration of 13, 14-dihydro-15-Keto Prostaglandin $F2^{\alpha}$ (PGFM), increased activity of Creatine Kinase (CK), Lactic Dehydrogenase (LDH) and Sorbitol dehydrogenase (SH) and decreased concentration of fibrinogen. Intravenous injection of meloxicam, a non-steroidal anti-inflammatory drug at a dose of 0.5 mg kg^{-1} body weight prior to endotoxin administration significantly ($p<0.05$) reduced maxim temperature and duration of fever induced by endotoxin. The drug also significantly decreased prostaglandin production but produced no significant effect changes of fibrinogen or enzymes activity, induced by endotoxin injection. It is suggested that meloxicam could prophylactically inhibits endotoxin-induced fever and prostaglandin production in camels.

Key words: Endotoxin, meloxicam, camels, prostaglandins, fibrinogen, enzymes, Saudi Arabia

INTRODUCTION

Septic-like shock conditions could be induced in camels by administration of endotoxin Lipopolysaccharide (Al-Dughaym, 2004; Al-Dughaym and Homeida, 2008). Endotoxin elicits a release of cytokines by macrophages (Gabay and Kushner, 1999). These cytokines orchestrate many of the inflammatory reactions related to endotoxaemic states (Ohtsuka *et al*., 1997). The responses include blood chemical and hormonal changes like leucopenia, decreased levels of several ions, activation of adreno-pitutary axis (Lohuis *et al*., 1988) and activation of the arachidonic acid cascade with increased synthesis of prostaglandins (Oslon *et al*., 1995). A better understanding of the basic pathophysiology of endotoxaemia in camels is a pre-requisite to enhancing therapeutic effectiveness of endotoxaemia in clinical patients. Potential therapeutic modalities for treatment of endotoxaemia shock include agents that block release of arachidonic acid metabolites (Oslon *et al*., 1995; Al-Dughaym and Homeida, 2010). The objective of this study was to investigate the prophylactic effect of meloxicam, a Non-Steroidal Anti-Inflammatory (NSAID) and prostaglandin synthesizing inhibitor (Oslon *et al*., 1995) in endotoxin treated camels.

MATERIALS AND METHODS

Animals: About 15 Arabian camel calves 3-4 months of age were used in the study. Animals have free access to their mother's milk and water. Animals were divided equally into 3 groups:

Group 1: Animals were injected with saline and used as controls.

Group 2: Animals were given a single dose of 0.01 mg kg^{-1} body weight Lipopolysacchoride endotoxin of *E. coli* serotype 055: B5 (Sigma Chemicals, UK).

Group 3: Animals were given a bolus intravenous injection of meloxicam (Metacam Vet. 5 mg mL^{-1}, Boehringer-Ingelheim, Sweden) at a dose of 0.5 mg kg^{-1} body weight followed by injection of endotoxin 90 min later.

Clinical signs: Rectal temperature was recorded at hourly interval for the 1st 24 h post endotoxin or saline treatments.

Collection of blood samples: Blood samples were collected into plain tubes. Serum was separated and stored at -20°C until analysis.

Analysis of samples: Creatine Kinase (CK), Lactic Dehydrogenase (LDH) and Sorbitol Dehydrogenase (SH) were monitored by blood. Chemistry auto analyser (Dade Behring Inc. Deerfield, IL, USA). Fibrinogen concentration was assayed using commercial Kit (Diagnostic Stago, Roche, Basilea, Switzerland). The concentration of prostaglandin $F2^{\alpha}$ metabolite, 13, 14-dihydro-15-Keto Prostaglandin 2a (PGFM) in the plasma was estimated by Radioimmunoassay (RIA) as previously described (Homeida and Klalafalla, 1987). The inter and intra-assay

coefficients of variation were 8.2% (n = 11) and 11.3% (n = 10), respectively for PGFM. Assay sensitivity was 45 pg mL^{-1} for PGFM.

Statistical analysis: Data were expressed as means±SD. Analysis of Variance (ANOVA) for repeated measures using General Linear Model (GLM) procedure of the Statistical Analysis System (SAS) was used to test the effect of endotoxin. Comparison of means in different groups was made by Duncan's multiple-range test, $p<0.05$ was accepted as statistically significant.

RESULTS

The changes in body temperature after intravenous injection of saline endotoxin and meloxicam are shown in Table 1. Maximum body temperature was reached at 4h after injection of endotoxin (group 2) or meloxicam and endotoxin (group 3). Significantly ($p<0.05$) higher temperature was observed in endotoxin group (group 2) compared to saline (group 1) or meloxicam and endotoxin (group 3). The duration of fever was 9 h in group 2, significantly ($p<0.05$) >4 h in group 3.

Results of PGFM, fibrinogen and enzymes activity is shown in Table 2. Endotoxin significantly ($p<0.05$) increased PGFM and the activity of CK, LDH and SH in group 2 animals compared to group 1 and 3 animals. A significant ($p<0.05$) decrease in the fibrinogen concentration was observed in endotoxin treated animals compared to saline or meloxicam and endotoxin treated animals.

Table 1: Rectal temperature during the 1st 24 h post endotoxin or saline treatment in camels

	Treatments (N)		
Parameters	Saline	Endotoxin	Meloxicam+ endotoxin
Maxim temperature (°C)	38.9±0.5[a]	41.7±0.6[b]	40.3±0.3[a]
Time to maximam temperature (h)	0[a]	4[b]	4[b]
Duration of fever (h)	0[a]	9[b]	4[c]

Values in the rows having different superscripts differ significantly ($p<0.05$)

Table 2: Effect of injection of saline, endotoxin or meloxicam on blood 13, 14-dihydro-15-keto prostaglandin $F2^{\alpha}$ (PGFM) and fibrinogen concentration and enzyme activity 6hours after administration in camels

	Treatment (N)		
Parameters	Saline (5)	Endotoxin (5)	Endotoxin+ Meloxicam (5)
PGFM (pgmL)	105±25[b]	1850±25[b]	125±12[a]
Fibrinogen (g d^{-1} l)	0.32±0.03[a]	0.22±0.02[b]	0.23±0.02[b]
Creatine Kinase (μ L^{-1})	140.8±9.9[a]	430.4±26.1[b]	31.0±16.2[c]
Lactic dehydrogenase (μ L^{-1})	210.1±8.6[a]	406.1±14.3[b]	320±12.1[c]
Sorbitol dehydrogenase (μ L^{-1})	2.6±0.3[a]	19.3±0.5[b]	10.2±0.4[c]

Values in the rows having different superscripts differ significantly ($p<0.05$)

DISCUSSION

Intravenous administration of endotoxin has produced fever and increased production of prostaglandins in camels. Similarly, endotoxin via its cytokines pathway has produced increased production of prostaglandins in pregnant camels (Al-Dughaym and Homeida, 2010), cows (Konigsson *et al*., 2002) and in a number of cell types like polymorph nuclear, mononuclear and endothelial cells (Vane and Botting, 1996).

These prostaglandins are believed to act as central pyrogenic agents (Ushikubi *et al*., 1998). Meloxicam has produced decreased prostaglandin production and consequently reduced maximum temperature and fever induced by endotoxin. Meloxicam suppresses endotoxin-induced fever and prostaglandin production in heifers (Konigsson *et al*., 2002) and cats (Justus and Quirke, 1995). Endotoxin has induced increased activity of serum CK, LDH and SH as reported elsewhere for the calves (Sharma *et al*., 2003). A rise in CK is indicative of myopathy (Cadenas *et al*., 1998), LDH is indicative of cardiac and Liver damage and SH is specific for liver injury caused by myodegenerative and anoxia primarily due to endotoxic shock (Wright *et al*., 1981; Kaszubkiewlez *et al*., 1981; Cadenas *et al*., 1998). A significant decrease in the fibrinogen concentration was observed during endotoxaemia in camels. Gadwin and Schaer (1989) reported hypo fibrinogenemia, prolonged coagulation times and elevation of fibrin degradation products during septic shock.

CONCLUSION

Meloxicam has no distinct beneficial effect on enzyme and fibrinogen changes produced due to endotoxic shock in camels.

In this study, it is suggested that meloxicam could prophylactically inhibits endotoxin-induced fever and prostaglandin production in camels.

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