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RESEARCH ARTICLE

Effect of meloxicam on serum vitamin and cytokine levels during endotoxemia

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Özet

Yurt AO. Meloksikamın endotoksemide serum vitamin ve sitokin düzeylerine etkisi. **Eurasian J Vet Sci, 2012, 28, 1, 47-53**

Amaç: Araştırmanın amacı lipopolisakkarit ile oluşturulan endotoksemide meloksikam uygulamasının serum vitamin ve sitokin düzeylerine etkisini belirlemektir. Ayrıca serum biyokimyasal parametreler de değerlendirildi.

Gereç ve Yöntem: Araştırmada elli yetişkin erkek Sprague Dawley rat kullanıldı. Beş adet rat 0 zaman örneklemeyi elde etmek için ayrıldıktan sonar kalan ratlar 3 eşit gruba ayrıldı. Birinci gruba lipopolisakkarit (4 mg, intraperitoneal), ikinci gruba meloksikam (50 mg/kg, intraperitoneal) ve üçüncü gruba lipopolisakkarit (4 mg, intraperitoneal) + meloksikam (50 mg/kg, intraperitoneal) uygulandı. Kan örnekleri 2., 4. ve 8. saatlerde alındı. Serum retinol, β-karoten, vitamin C, interlöykin-1α, interlöykin-1β, interlöykin-2 ve rutin biyokimyasal parametreler ölçüldü.

Bulgular: Lipopolisakkarit uygulaması sonrasında düşen β-karoten düzeyi ($p<0.05$) meloksikam tarafından engellenirken, artan interlöykin-1α düzeyi engellenemedi ($p<0.05$). Lipopolisakkarit kalp, karaciğer ve böbrek hasar belirteçleri ile kolesterol ve trigliserit düzeylerini artırırken ($p<0.05$), meloksikam uygulaması kreatin kinaz-MB ile kolesterol düzeylerindeki artışları engellerken üre ve trigliserit düzeyini daha fazla yükselmesine neden oldu.

Öneri: Endotokseminin akut döneminde uygulanan meloksikam, vitamin kayıplarını ve kalp hasarını önlemede etkili olabilir. Ayrıca endotokseminin tedavisinde nonsteroid anti-enflamatuar ilaç ile vitamin ilaveleri faydalı olabilir.

Abstract

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Aim: The aim of this study is to evaluate the effects of meloxicam on serum vitamin and cytokine levels during lipopolysaccharide-induced endotoxemia. Serum biochemical concentrations were also evaluated.

Materials and Methods: Fifty male adult Sprague Dawley rats were used in this research. Five rats were reserved to obtain 0 time data then the rest were divided into 3 equal groups. First group received lipopolysaccharide (4 mg, intraperitoneal), second group received meloxicam (50 mg/kg, intraperitoneal) and third group received lipopolysaccharide (4 mg, intraperitoneal) plus meloxicam (50 mg/kg, intraperitoneal). Blood samples were collected at 2, 4 and 8 hours after administrations. Serum retinol, β-carotene, vitamin C, interleukin-1α, interleukin-1β, interleukin-2 and routine biochemical values were measured.

Results: After lipopolysaccharide administration, decreased β-carotene level ($p<0.05$) was inhibited by meloxicam while increased interleukin-1α level ($p<0.05$) could not. Lipopolysaccharide caused increase in damage indicator levels of heart, liver, kidney besides cholesterol and triglyceride ($p<0.05$) while meloxicam administration was inhibited increase in creatine kinase-MB and cholesterol levels but caused more increase in urea and triglyceride levels.

Conclusion: Meloxicam may be useful in inhibiting vitamin loses and heart damage. In addition, non-steroidal anti-inflammatory drug and vitamin supplementation may be useful during acute phase of endotoxemia.

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► Introduction

Lipopolysaccharide (LPS, endotoxin), a part of Gram-negative bacteria cell wall, causes endotoxemia. LPS affects macrophages and endothelial cells directly and causes release of cytokines, eicosanoids, free oxygen radicals, platelet activating factor and these events have role in physiopathology of septic shock (Jean-Baptiste 2007). LPS is being used in modeling all kinds of infections from local inflammatory model (Er and Yazar 2010) to septic shock (Yazar et al 2010a).

Vitamins are organic substances that required for having metabolic events under optimal physiological conditions and maintaining healthy situation, generally are not synthesized in body and have to be taken by foods. There are two groups of vitamins as oil solubles (A, D, E, and K) and water solubles (C and B complex). Vitamin C (ascorbic acid) is not synthesized in body of human, primates and rat. Vitamin C is the most available vitamin in polymorphonuclear leukocytes and needed for optimal functioning of this cell. Vitamer in foods is the common name for a number of active molecules including vitamin A precursors. The most available vitamers in the body are retinol (vitamin A) and 3-dehidroretinol (vitamin A2). Their precursors are α, β and μ carotenes (Baspinar et al 1998, Kayaalp 2009). Retinol and β-carotene are necessary for increasing phagocytosis ability of peritoneal macrophages, developing immunoglobulin synthesis of plasma cells and protection of structural integration of lenfoid organs. Vitamin A stimulates interleukin (IL) 1 and IL-2 production, T-cell activity, humoral immunity and inhibits immunosuppressive effects of cortisol (Chew 1987, Mammadov 2002).

Cytokines are the first actors of immune response, released from phagocytes stimulated by microorganisms and defined as pro-inflammatory or anti-inflammatory cytokines depending on their effects. Interleukin-1, a proinflammatory cytokine, has two sub types as IL-1α and IL-1β. Both types of IL-1 are biologically active and have similar effects. Released IL-1 causes vasodilatation, hypotension, increased pain sensitivity and lymphocyte activation (Gerard et al 2004, Gouwy et al 2005, Feldmeyer et al 2010). IL-2 (lymphokine) is released by lymphocytes and has role in T-cell proliferation and their immune response. Later researches have showed that they have effects on natural killer cells, B cells, monocytes and neutrophils. After discovering that IL-2 stimulated natural killer cells terminates tumor cells, IL-2 levels may be used as cancer indicator or can be used in its treatment (Fehniger et al 2002).

Multi organ failure is insufficient contribution of one or more organs in homeostasis mechanism, and death usually happens due to organ failures. Mitochondrial dysfunction, disseminated intravascular coagulation, corrupted tissue oxygenation and oxidative damage in endotoxemia causes organ failure (Titheradge 1999, Fujita et al 2004, Simkova et al 2007). Serum troponin I, creatine kinase-MB (Ck-MB) and myoglobin levels are accepted in determining heart damage, while alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyl transferase (GGT) levels are taken into consideration as liver damage indicators. Increased cardiac and hepatic damage indicators were reported in the endotoxemia (Er et al 2010a, Yazar et al 2010a). Blood urea nitrogen (BUN) and creatinine levels are accepted as kidney function tests. It is often reported that kidney incompetence is developed and BUN and creatinine levels are increased in endotoxemic individuals (Elmas et al 2006, Elmas et al 2008). It is also reported that lipid metabolism is frequently affected during endotoxemia (Er and Yazar 2010).

Meloxicam (MLX) is a non-steroidal anti-inflammatory drug (NSAID) of oxicam class. Although it is not a selective cyclooxygenase (COX2) inhibitor, inhibits COX2 twelve times more than COX1. Usually single daily dose is enough for most of the species and its bioavailability after parenteral administration is approximately 100%. Usually, no dose adjustment is necessary in case of kidney or liver incompetency. MLX is prescribed both in human and veterinary medicine. A NSAID is suggested in treatment of infection or endotoxemia (Davies et al 1999, Fosslien 2005, Smith 2005, Tras and Elmas 2009).

It has been hypothesized that inhibition synthesis of COX2, which has important role in systemic inflammatory response developed during endotoxemia, by a strong specific COX2 inhibitor such as MLX may have useful effects.

The aim of this study is to determine the effect of MLX on levels of serum vitamin, cytokine and routine biochemical parameter levels which are supposed to change after LPS administration, thus evaluating its indication in endotoxemia or septic shock cases.

► Materials and Methods

Fifty Sprague Dawley male adult rats (200-280 g, Experimental Medicine Research and Practice Centre, Selcuk University, Konya) were used in this research. Research procedure was approved by Ethical Committee of Veterinary Faculty of Selcuk University. Five rats were reserved to obtain 0 time data then the rest were divided into 3 equal groups in order to perform applications below. First group (n=15) received LPS (4 mg, intraperitoneal, Escherichia coli 0111:B4, Sigma-Aldrich Chemie, Germany) (Altan et al 2010), second group (n=15) received MLX (50 mg/kg, intraperitoneal, Vetcam Inj., Cipla Ltd., India) (Goren et al 2009) and third group (n=15) received LPS (4 mg, intraperitoneal) plus meloxicam (50 mg/kg, intraperitoneal). Intracardiac blood samples were collected under thiopental sodium (70 mg/kg, intraperitoneal, Pental Sodyum 1 g Inj. Sol., I. E. Ulagay Ilac Sanayi Turk A.S., Topkapi, Istanbul, Turkey) anesthe-

sia following 2, 4 and 8 hours after administrations. Serum retinol, β-carotene (Suzuki and Katoh 1990) and vitamin C (Kyaw 1978) levels were analyzed by using ELISA spectrophotometer reader (MWGt Lambda Scan 200, USA). Serum IL-1α (eBioscience, San Diego, CA, USA), IL-1β (eBioscience, San Diego, CA, ABD) and IL-2 (eBioscience, San Diego, CA, USA) levels were analyzed by using commercial kits in ELISA spectrophotometer reader.

Serum Ck-MB, ALP, AST, GGT, BUN, creatinine, cholesterol, triglyceride, high density lipoprotein (HDL), low density lipoprotein (LDL), amylase, total protein, albumin and calcium levels were determined by autoanalyzer (Tokyo Boeki Prestige 24i, Japan).

Data are expressed as mean ± SE. The results were analyzed by ANOVA and Tukey multiple range test (SPSS 12.0). $P<0.05$ was accepted as the criterion for statistical significance.

► Results

The effects of MLX on serum retinol, β-carotene, vitamin C and cytokine levels in healthy and endotoxic rats are presented in Table 1, and its effects on biochemical values are shown in Table 2. LPS administration decreased serum β-carotene level ($p<0.05$) and this decrease was inhibited by MLX, while MLX had no inhibitory effects on increase of IL-1α ($p<0.05$) and IL-1β ($p>0.05$) levels (Table 1). LPS administration caused increase in damage indicator levels of heart (Ck-MB), liver (GGT), kidney (BUN) besides cholesterol and triglyceride ($p<0.05$) while MLX administration was inhibited increase in Ck-MB and cholesterol levels but caused more increase in BUN and triglyceride levels (Table 2). Other parameters (LDL, amylase, albumin, calcium) with statistically important difference were within limits reported for healthy rats (Table 2).

► Discussion

Inflammation mediators, mitochondrial dysfunction, disseminated intravascular coagulation, corrupted tissue oxygenation and oxidative damage occurred during endotoxemia may cause organ dysfunction (Smith 2005, Simkova et al 2007, Yazar et al 2010b).

In this research, LPS administration did no effect on serum vitamin C and retinol levels ($p<0.05$) while decreased β-carotene level and this decrease was inhibited by MLX (Table 1). Decreased serum β-carotene level was reported after vaccination and during sepsis (Yalcin et al 1998, Berger and Chiolero 2007). β-carotene is stored in liver, and it shows antioxidant activity (Palozza and Krinsky 1991) following oxidative damage caused by LPS administration (Yazar et al 2010a) and stimulated nuclear factor may present anti-inflammatory effect by inhibiting activity of kappa B (NF-κB) thus reducing synthesis of nitric oxide, prostaglandin and cytokines (Bai et al 2005). Decreased serum retinol level in the acute infection may be due to increase of its excretion by urine (Stephensen et al 1994), its antioxidant activity and its utilization for inhibiting activity of NF-κB. In this research, MLX inhibited the decrease of β-carotene level caused by LPS (Table 1). No information found in literature about effects of MLX on β-carotene levels in infected or healthy organisms. However, flunixin, another NSAID being used frequently in veterinary medicine, did not inhibit decrease in serum vitamin C level of endotoxic rats (Er et al 2010a). This result shows that MLX may be more effective in preventing vitamin loses during infections.

In the present research, LPS administration increased IL-1α ($p<0.05$) and IL-1β ($p>0.05$) levels while had no effect on IL-2 concentration (Table 1). Many researchers reported that levels of proinflammatory cytokines such as IL-1 increased following LPS administration (Uney et al 2009, Er et al 2010b). It was found that MLX administration did not decreased high IL-1 levels (Table 1). Although MLX has no effect on expression of TNFα, a proinflammatory cytokine, (Martin et al 2008), flunixin inhibits increased proinflammatory cytokine levels after LPS administration (Yazar et al 2007). These results show that effects of NSAIDs on cytokine synthesis may differ individually.

In this research, LPS administration increased damage indicator levels ($p<0.05$) of heart, liver and kidney (Table 2). LPS administration increases levels of serum biochemical parameters in ponies (Ewert et al 1985), liver and kidney damage indicators in rabbits (Elmas et al 2006a, Elmas et al 2008), heart and kidney damage indicators in rats (Er and Yazar 2010, Yazar et al 2010a) with endotoxemia. In this research, MLX administration totally inhibited increase of Ck-MB level occurred following LPS administration (Table 2). While the safety of selective COX2 inhibitors and other NSAIDs for heart is disputable, MLX is reported to be safer than diclofenac, naproxen and proxicam (Fosslien 2005). Nimesulid may have protective effect against experimental myocardial infarctus of rabbits, and rofecoxib, a COX2 inhibitor, decreases Ck-MB and troponin I levels in experimental acute heart ischemia of dogs (Saeed and Ahmed 2005, Carnieto et al 2009). This protective effect may be due to its preventive effect against necrosis formation in heart (Carnieto et al 2009). These results show that the effect of NSAID on heart may be different according to the kind and dose of the drug used, the animal species and the type of heart disease. Although MLX administration did not decreased damage indicator levels of liver and kidney down to levels of those in healthy rats, it was determined that increased GGT level in LPS group was decreased by MLX administration (Table 2). It was reported that due to its antioxidant effects, MLX administration may prevent liver damage in rats induced by cocaine or cocaine and LPS administration (Visalli et al 2008). It was found that

Table 1. Effect of meloxicam on the serum vitamin and cytokine concentrations of healthy and endotoxemic rats (mean±SE).

Parameters	Groups	Control (0. hour)	2 hours	4 hours	8 hours
Vitamin C mg/dL	MLX (50 mg/kg, IP)	1.52±0.21	1.76±0.54	2.08±0.36	2.07±0.22
	LPS (4 mg/kg, IP)	1.52±0.21	1.49±0.29	0.98±0.26	0.99±0.18
	LPS+MLX	1.52±0.21	1.30±0.22	0.80±0.21	1.78±0.41
Retinol µg/dL	MLX (50 mg/kg, IP)	29.3±1.51	26.7±1.32	26.6±0.99	26.5±1.18
	LPS (4 mg/kg, IP)	29.3±1.51	27.5±0.95	27.5±1.74	25.0±0.47
	LPS+MLX	29.3±1.51	28.6±1.64	24.1±1.61	24.7±1.17
β-carotene µg/dL	MLX (50 mg/kg, IP)	14.8±1.15	12.7±0.56	13.9±1.11	12.8±0.52
	LPS (4 mg/kg, IP)	14.8±1.15^{A}	12.4±0.67^{AB}	12.8±1.07^{AB}	10.4±0.99^{B}
	LPS+MLX	14.8±1.15	14.3±1.59	13.7±0.34	12.9±0.60
Interleukin-1α pg/mL	MLX (50 mg/kg, IP)	71.4±19.8	77.3±5.83	168±74.6	26.6±11.6
	LPS (4 mg/kg, IP)	71.4±19.8^{B}	341±132B^{B}	633±201^{AB}	1079±247^{A}
	LPS+MLX	71.4±19.8^{B}	431±193^{AB}	768±163^{A}	381±149^{AB}
Interleukin-1β pg/mL	MLX (50 mg/kg, IP)	6.60±6.60	0.00±0.00	0.00±0.00	17.3±17.3
	LPS (4 mg/kg, IP)	6.60±6.60	203±49.9	309±100	329±173
	LPS+MLX	6.60±6.60^{B}	376±169^{B}	1144±284^{A}	410±109^{B}
Interleukin-2 pg/mL	MLX (50 mg/kg, IP)	60.7±43.7	80.9±13.5	171±91.4	286±139
	LPS (4 mg/kg, IP)	60.7±43.7	153±68.0	162±28.8	34.1±20.9
	LPS+MLX	60.7±43.7	36.4±13.3	142±42.2	103±46.5

MLX; meloxicam, LPS; lipopolysaccharide. $^{A, B}$: Different letters in the same line are statistically significant (Tukey test, p<0.05).

MLX administration increased BUN level in healthy rats and this increase was more severe when administrated together with LPS (Table 2). Increased level of kidney damage indicator in healthy rats by MLX may be due to causing acute kidney damage (Lascelles et al 2007) by decreasing peritubular capillary blood irrigation (Tanaka et al 2008). More increase in BUN level after administration of MLX plus LPS, may be due to association of nephrotoxic effect of MLX with LPS induced acute kidney damage.

It was determined that LPS administration increased serum cholesterol and triglyceride levels and MLX administration inhibited increase in cholesterol level while had no effect on triglyceride increase (Table 2). Increased triglyceride levels after LPS administration (Er and Yazar 2010) may be due to increased hepatic synthesis of triglycerides and/or their decreased hepatic clearance (Berbee et al 2005), inhibiting oxidation of free fatty acids (Maitra et al 2009) or increasing quantity of free fatty acids directly by generating lipolysis in adipose tissue (Zu et al 2009) during endotoxemia. Although plasma cholesterol level may decrease during sepsis (Berbee et al 2005), it was found in this research (Table 2) and reported by some other researchers that blood cholesterol level increased after LPS administration (Elmas et al 2008, Er and Yazar 2010). Increase of cholesterol level may be due to lipolysis of adipose tissue caused by LPS (Zu et al 2009), thus increased quantity of free fatty acids. No literature might be reached about direct effect of MLX on cholesterol and triglyceride levels during endotoxemia. However, strong anti-inflammatory effect of MLX (Tras and Elmas 2009) may inhibit production of inflammatory mediators (Bednarek et al 2005) thus may contribute in protection of general homeostasis.

► Conclusions

MLX administration may be useful in avoiding β-carotene loses and decreasing high IL-1 level during endotoxemia, however it has a partial effect on adjusting incurred multiple organ dysfunctions and lipid metabolism. A NSAID administration and vitamin supplementation during acute phase of endotoxemia may be useful.

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Table 2. Effect of meloxicam on the serum biochemical values of healthy and endotoxemic rats (mean±SE).

Parameters	Groups	Control (0. hour)	2 hours	4 hours	8 hours	Healthy rat values	References
Ck-MB U/L	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	1838±146 1838±146^{B} 1838±146	1995±270 1708±249^{B} 1774±417	3245±361 4043±1220^{AB} 2160±578	2854±542 6130±1080^{A} 1603±281	978-2230	Singh et al 2008, Mo et al 2010.
ALP U/L	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	335±44.3 335±44.3^{AB} 335±44.3^{AB}	274±39.2 309±38.1^{AB} 223±35.4^{B}	275±33.7 233±32.9^{B} 335±20.5^{AB}	230±34.6 406±44.1^{A} 434±77.4^{A}	214-408	Ozbek et al 2005, Ozbek et al 2006.
AST U/L	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	347±72.9 347±72.9 347±72.9	275±65.2 229±31.9 175±24.0	401±28.0 277±66.3 236±43.2	269±45.6 405±61.9 342±75.8	157-674	Ghule et al 2009, Er and Yazar 2010.
GGT U/L	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	5.00±0.24 5.00±0.24^{B} 5.00±0.24^{B}	4.60±0.97 4.40±0.50^{B} 4.40±0.81^{B}	4.20±0.58 5.00±2.16^{B} 9.00±1.04^{A}	3.00±0.31 21.4±7.11^{A} 10.4±1.12^{A}	0.7-6.7	Helal 2010, Yazar et al 2010a.
Creatinine mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	0.55±0.03^{A} 0.55±0.03^{AB} 0.55±0.03^{B}	0.48±0.01^{AB} 0.46±0.03^{B} 0.44±0.01^{B}	0.44±0.01^{B} 0.52±0.04^{AB} 0.54±0.03^{B}	0.54±0.03^{A} 0.64±0.04^{A} 0.85±0.05^{A}	0.2-0.8	Yarsan and Durgut 2010.
BUN mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	52.8±4.04^{B} 52.8±4.04^{B} 52.8±4.04^{B}	70.2±2.85^{AB} 59.6±4.33^{B} 66.0±4.12^{B}	88.6±3.70^{A} 71.6±13.4^{AB} 111±4.80^{A}	86.8±9.50^{A} 103±14.9^{A} 131±9.46^{A}	36-53	Er and Yazar 2010, Senturk et al 2010.
Triglyceride mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	67.8±10.8 67.8±10.8^{B} 67.8±10.8^{B}	64.8±9.93 84.0±8.14^{B} 88.4±12.2^{B}	61.2±9.15 126±31.6^{AB} 104±4.14^{B}	65.0±6.26 177±17.1^{A} 216±45.1^{A}	60-145	Ness 2004, Lok et al 2010.
Cholesterol mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	112±5.95 112±5.95^{B} 112±5.95	95.8±14.0 94.8±9.75^{B} 114±4.26	106±9.14 111±4.89^{B} 108±19.3	97.2±12.1 156±17.5^{A} 121±12.7	57-130	Ness 2004, Er and Yazar 2010.
HDL mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	25.6±3.55 25.6±3.55 25.6±3.55	21.0±2.93 22.4±1.32 24.0±2.00	22.4±2.80 22.0±1.92 23.2±2.59	18.0±1.22 16.8±2.51 17.8±0.86	17-32	Celik and Yilmaz 1999, Tasgin et al 2010.
LDL mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	16.4±2.03^{A} 16.4±2.03^{B} 16.4±2.03^{B}	12.2±0.37^{AB} 11.8±1.31^{B} 13.0±1.94^{B}	10.4±1.02^{B} 11.8±0.96^{B} 11.0±0.54^{B}	16.0±1.00^{A} 29.2±0.58^{A} 23.8±2.05^{A}	7.30-29	Celik andYilmaz 1999, Akkaya and Celik 2010.
Amylase U/L	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	1117±83.5 1117±83.5 1117±83.5^{AB}	1051±161 1166±27.0 1363±52.3^{A}	965±71.2 1147±52.8 1140±119^{AB}	756±103 916±104 859±74.1^{B}	814-1724	Gokalp et al 2005, Tasgin et al 2010.
Total protein g/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	5.86±0.16 5.86±0.16 5.86±0.16	5.88±0.16 5.20±0.14 5.92±0.13	5.58±0.11 5.80±0.41 5.94±0.17	5.28±0.19 5.62±0.10 5.66±0.09	4.7-8.1	Yarsan and Durgut 2010.
Albumin g/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	3.10±0.07 3.10±0.07^{A} 3.10±0.07^{A}	3.14±0.08 2.68±0.14^{B} 2.94±0.08^{AB}	2.94±0.06 2.88±0.06^{AB} 2.98±0.07^{AB}	2.72±0.07 2.90±0.06^{AB} 2.80±0.04^{B}	2.7-5.1	Yarsan and Durgut 2010.
Calcium mg/dL	MLX (50 mg/kg, IP) LPS (4 mg/kg, IP) LPS+MLX	10.5±0.28 10.5±0.28^{A} 10.5±0.28^{A}	9.86±0.45 9.26±0.09^{B} 10.4±0.18^{A}	10.4±0.17 10.2±0.20^{A} 10.4±0.11^{A}	9.98±0.14 9.38±0.05^{B} 9.24±0.34^{B}	8.80-13.0	Ness 2004, Tasgin et al 2010.

MLX; meloxicam, LPS; lipopolysaccharide, Ck-MB; creatinin kinase-MB, ALP; alkalen phosphatase, AST; aspartat aminotransferase, GGT; gamma glutamyl transferase, creatinine, BUN; urea, HDL; high density lipoprotein, LDL; low density lipoprotein. $^{A, B}$: Different letters in the same line are statistically significant (Tukey test, $p<0.05$).

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