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Effects of Marbofloxacin and Ketoprofen on Some Biochemical and Coagulation Parameters in Calves

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ABSTRACT

Marbofloxacin (MBX) is a 3rd generation fluoroquinolone specifically developed for animal health and is an approved antimicrobial agent for the cure of mastitis and respiratory diseases in cattle and swine. Ketoprofen (KTP) is a nonsteroidal anti-inflammatory drugs (NSAID) belonging to the aryl propionic acid group and is used in musculoskeletal inflammation and pain, abdominal pain and other inflammatory circumstances. The objective of this study is to investigate the impact of simultaneous administration of MBX and KTP on the coagulation and biochemical parameters in calves. In the study, 18 clinically healthy calves were randomly separated into 3 groups of six animals each. The first group of calves received a single dose of MBX at 8 mg/kg, the second group received MBX at 8 mg/kg along with concurrent KTP at 3 mg/kg and the third group received only KTP at 3 mg/kg dose. The drugs were administered via intramuscular (IM) injection in the neck region. Biochemical and coagulation parameters were evaluated using an automated analyzer and coagulation analyzer, respectively. The IM injection of MBX into calves significantly increased creatine kinase (CK) and lactate dehydrogenase (LDH) values, which may be related to muscle damage. This may limit the administration via IM route of MBX to calves. KTP increased the prothrombin time (PT) and activated partial thromboplastin time (aPTT) values but decreased the fibrinogen value. It can be stated that in alone MBX, and KTP administration and their combination, further investigations are required to determine the safety of drugs after repeated administrations and other administration routes in calves.

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INTRODUCTION

MBX, a 3rd generation fluoroquinolone developed exclusively for veterinary medicine, is an antimicrobial agent with high activity against gram-positive and gram-negative bacteria, including and Mycoplasma **(Sidhu, *et al.*, 2010; Fernández, *et al.*, 2021).** Acting by blocking bacterial DNA topoisomerase II and IV, MBX is approved in the European Union (EU) for the cure of mastitis and respiratory diseases in cattle and pigs **(Martínez, *et al.*, 2006; Lei, *et al.*, 2017).** While the European Medicines Agency (EMA) recommendations a dosing schedule of 2 mg/kg for 3-5 days for the cure of mastitis and respiratory infections, studies have demonstrated that a once-through of 8 mg/kg is effective **(Grandemange, *et al.*, 2017; Patil, *et al.*, 2021).** While it is less than 10% bound to plasma proteins in humans, laboratory animals and pigs; this ratio is about 30% in cattle. It is mostly excreted in the urine **(EMA, 1999).** KTP, a member of the aryl propionic acid group of NSAIDs, is recommended for use in cattle, horses, dogs, cats, and sheep for the treatment of musculoskeletal inflammation and pain, abdominal pain, and other inflammatory conditions. The recommended dose of KTP for cattle is 3 mg/kg **(Papich, 2021).**

Combined use of NSAID group drugs and antibiotics is recommended in cases of endotoxemia, respiratory diseases, urinary and bone system diseases, postoperative inflammation, cataract infection and other infections. However, drug interactions may occur at the distribution, metabolism, or excretion level as a result of the combined use of drugs **(Deleforge, *et al.*, 1994; Thomas and Puleo, 2011).** Drug interactions that

occur due to the concurrent use of drugs during treatment can lead to unforeseen alterations in the body's disposition of drugs. These alterations can lead to the emergence of resistance to antimicrobial drugs, the occurrence of adverse effects and suboptimal drug exposure, resulting in the inadequacy of infection treatment **(Roberts, *et al*., 2012; Jager, *et al.* 2016;).**

Although fluoroquinolones are generally considered effective and reliable drugs, they have serious side effects such as tendon rupture, joint pain, extremity pain, neuropathies associated with paresthesia, visual and auditory disturbances, taste, and smell disorders, phototoxicity, hematological effects, eosinophilia effect in the liver, hypoglycemia and CYP 450 inhibition **(Rusu, *et al.*, 2023).** Serious side effects may occur during NSAID therapy, among which are gastrointestinal ulceration, liver and kidney damage, and myocardial infarction. The safety of drugs is important and changes in serum biochemical and coagulation markers may provide an early indicator of cellular toxicity **(Lascelles, *et al.*, 2005; Er, *et al.*, 2013;).** In the literature review, no study was found on the effect of concurrent administration of MBX and KTP on biochemical and coagulation markers of calves. The objective of this study is to investigate the effect of MBX and KTP concomitant administration on coagulation and biochemical parameters (urea, creatinine, AST, ALT, CK, albumin, LDH, PT, aPTT, D-Dimer) in calves.

MATERIALS AND METHODS

Animals

The study was carried out in a private farm in the Kadınhanı district of Konya province, Turkey. The study was conducted on 18 Holstein calves (2-3 months old, 81-98 kg) that were considered to be healthy in the general clinical inspection and had not received any medication treatment in the one month before the study. Calves were housed in individual calf huts. Calves were fed milk substitutes, roughage and concentrates supplemented with vitamins and minerals.

Ethical approval

All procedures on calves were approved by the Local Ethics Committee for Animal Experiments at Selcuk University with the approval number 2022/139.

Experimental design

A total of 18 calves were randomly separated into 3 groups, with six animals in each group. The first group received MBX (Marboforce® Injection Solution IPM, Turkey) alone at a dose of 8 mg/kg by a single intramuscular injection on the neck region. The second group of calves received 8 mg/kg MBX on the left side of the neck and 3 mg/kg KTP on the right side of the neck by intramuscular injection. The third group received only KTP (Ba-Keto® Injection Solution Bavet, Turkey) at a dose of 3 mg/kg by a single intramuscular injection on the neck region. In the study, blood samples were collected via jugular venipuncture at 0, 24 and 48 hours. Blood samples were collected into gel tubes (2 ml) for biochemical analysis and into sodium citrate tubes (2 ml) for coagulation tests. After centrifugation of the collected blood samples (3,500g x 10 min), the obtained serum and plasma samples were transferred to 2 ml Eppendorf tubes. Serum samples were stored in a deep freezer at -80°C until the day of analysis. The coagulation tests were carried out on the plasma samples within a time frame of 3 hours. The injection site was monitored for swelling, redness and pain, and the animals were followed clinically.

Analysis of biochemical and coagulation parameters

Biochemical parameters such as serum albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatine kinase (CK), Creatinine (CRE) and lactate dehydrogenase (LDH) levels were analyzed using an automated analyzer (Lab-300plus, Instrumentation Laboratory, Milan, Italy) from serum samples stored at -80°C. Coagulation factors consisting of prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen (FIB) and D-dimer were measured from plasma samples using a coagulation analyzer (Siemens, A-7799, Sysmex CA 1500, Germany).

Statistical analysis

The research data were presented as mean ± standard deviation (SD). Statistical analysis was conducted using the SPSS software (version 26.0, IBM). Biochemical and coagulation parameters were analyzed for homogeneity of variances. Values that showed normal distribution with *p-values* > 0.05 were considered for parametric statistical analysis. In both intragroup and intergroup comparisons of data, one-way analysis of variance (ANOVA) and *post-hoc Tukey* test were used (SPSS 26.0). $P < 0.05$ value was considered statistically significant.

RESULTS

No adverse reactions, general (in their feeding, drinking, defecation, and behavior) or local (pain, swelling, redness), were observed during clinical observation of calves following intramuscular administration of KTP and MBX.

The effects of single and simultaneous IM injections of MBX and KTP in calves on biochemical parameters are presented in Table 1. In the evaluation within the group, there was no statistically meaningful difference in ALB and BUN values in all groups (p>0.05). However, ALT values in the KTP group decreased at 24 and 48 hours compared to 0 hour (P<0.05). In MBX group, AST value at 24 hours was higher than that at 0 hour (P<0.05). CRE value increased significantly in the KTP group at the 48 hours compared to the 24 hours (P<0.05) and was similar to its level at the 0 hours at the 48 hours. CK value significantly increased at 24 hours compared to 0 hours in the MBX and MBX+KTP groups (P<0.05) but returned to the baseline level at 48 hours. LDH value increased significantly in the MBX and MBX+KTP groups at the 24 and 48 hours compared to the 0 hour (P<0.05). There was no statistically meaningful difference in ALB, BUN and CRE values between the groups (P>0.05). However, ALT, AST, CK and LDH value in in the MBX and MBX+KTP groups at 24 hours was significantly higher than that in the KTP group (P<0.05). In addition, the LDH value at 48 hours in the MBX and MBX+KTP groups was significantly higher than in the KTP group (P<0.05).

Table 1. The effects of single and simultaneous IM injections of MBX and KTP in calves on biochemical parameters. (n=6, mean ± SD)

Parameters	Sampling Time (Hour)	MBX (8 m/kg)	MBX+KTP (8mg/kg+3 mg/kg)	KTP (3 mg/kg)
ALB (g/L)	0	33.92±1.86	32.75±2.89	32.92±3.32
	24	33.50±5.35	32.58±9.47	31.67±4.05
	48	33.00±3.45	32.58±6.25	33.42±3.01
ALT (U/L)	0	9.33±2.27	10.00±3.03	11.50 ± 2.24^{x}
	24	10.50 ± 2.49^{a}	11.75 ± 3.06^{a}	$5.50\pm1.40^{b,y}$
	48	10.08±1.96	14.00±12.22	6.92 ± 1.20^{y}
AST (U/L)	0	38.33 ± 10.05^{y}	36.75±5.67	39.58 ± 4.18^{xy}
	24	$61.42\pm9.95^{a,x}$	59.59 ± 6.19^{a}	$35.50\pm2.61^{b,y}$
	48	54.50 ± 14.43^{xy}	60.08±28.78	43.33 ± 5.68^{x}
BUN (mg/dL)	0	22.00±2.26	21.08±3.14	22.42±3.07
	24	23.08±1.20	21.42±5.30	23.92±3.04
	48	20.83±3.60	18.58±4.34	23.42±5.35
CRE (mg/dL)	0	1.26±0.10	1.19±0.16	1.19 ± 0.12^{xy}
	24	1.30±0.4	1.34±0.45	1.09 ± 0.10^{y}
	48	1.21±0.23	1.19±0.23	1.29 ± 0.13^{x}
CK (U/L)	0	220.67 ± 49.46^{y}	226.67 ± 28.14^{y}	215.67±25.74
	24	$451.42\pm41.52^{a,x}$	$452.08\pm54.34^{a,x}$	224.08 ± 38.08^{b}
	48	258.58 ± 42.44^{y}	312.67 ± 85.57^{y}	236.67±40.80
LDH (U/L)	0	751.08 ± 83.52^{y}	709.08 ± 67.62^{y}	708.17±62.10
	24	$1218.92\pm151.04^{a,x}$	$1182.08\pm95.89^{a,x}$	730.92 ± 86.64^{b}
	48	$1059.33\pm175.85^{a,x}$	$1049.33\pm133.22^{a,x}$	707.42 ± 48.65^{b}

[a,b] Superscripts with different letters within the same row indicate significant differences between groups. (P < 0.05).
[x,y] Superscripts with different letters within the same column indicate statistically significant differences within the group. Superscripts with different letter in the same column show statistically significant differences (P < 0.05).
ALB; Albumin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, BUN; blood urea nitrogen, CRE; Creatinine, CK; creatine kinase, and LDH; lactate dehydrogenase.

The effects of single and simultaneous IM injections of MBX and KTP in calves on coagulation parameters are presented in Table 2. PT value significantly increased at 24 and 48 hours compared to 0 hours in the MBX+KTP and KTP groups (P<0.05). The aPTT value increased significantly in the KTP group at the 24 hours compared to the 0 hour (P<0.05) and decreased to its level at the 0 hour at the 48 hours. Fibrinogen value increased significantly in the MBX group at 24 hours compared to 0 hour (P<0.05) and decreased below the level of 0 hours at 48 hours (P<0.05). Fibrinogen value decreased significantly in MBX+KTP and KTP groups at 48 hour compared to 24 and 0 hours (P<0.05). D-Dimer value increased significantly in the KTP group at 24 and 48 hours compared to 0 hour (P<0.05). In intergroup comparison, PT value at 24 hours was significantly higher in the KTP group compared to the MBX group (P<0.05). The value of aPTT at 24 hours was significantly higher in the MBX+KTP and KTP groups compared to the MBX group (P<0.05). Fibrinogen value at 48 hour was significantly different in all groups (P<0.05). It was highest in MBX group and lowest in KTP group. Between the groups showed no significant statistical variance in their D-Dimer values (P>0.05).

Table 2. The effects of single and simultaneous IM injections of MBX and KTP in calves on coagulation parameters. (n=6, mean ± SD)

Parameters	Sampling Time (Hour)	MBX (8 m/kg)	MBX+KTP (8mg/kg+3 mg/kg)	KTP (3 mg/kg)
PT (sn)	0	31.58±2.24	$32.25±3.20^{y}$	$30.22±3.64^{y}$
	24	$35.70±4.33^{b}$	$40.12±3.62^{ab,x}$	$44.93±4.55^{a,x}$
	48	37.00±4.79	$43.25±5.46^{x}$	$42.12±4.99^{x}$
aPTT (sn)	0	49.65±4.79	50.15±4.19	$52.37±3.17^{y}$
	24	$50.60±1.60^{b}$	$55.50±8.35^{a}$	$59.87±5.63^{a,x}$
	48	48.47±4.16	48.81±2.77	$49.05±3.17^{y}$
Fibrinogen (g/L)	0	$2.81±0.25^{y}$	$2.76±0.24^{x}$	$2.96±0.20^{x}$
	24	$3.34±0.42^{x}$	$3.30±0.57^{x}$	$2.98±0.35^{x}$
	48	$1.58±0.10^{a,z}$	$1.39±0.12^{b,y}$	$1.24±0.05^{c,y}$
D-Dimer (ng/L)	0	466.50±78.33	521.00±101.09	$414.50±98.06^{y}$
	24	465.83±113.22	486.00±133.77	$560.83±95.55^{x}$
	48	493.83±71.36	527.17±114.99	$545.33±93.07^{x}$

^{a,b,c} Superscripts with different letters within the same row indicate significant differences between groups. (P < 0.05).
^{x,y,z} Superscripts with different letters within the same column indicate statistically significant differences within the group. (P < 0.05). PT; prothrombin time, aPTT; activated partial thromboplastin time.

DISCUSSION

Simultaneous administration of antibiotics and NSAIDs is recommended in the treatment of infection. However, concomitant use of these drugs may cause drug interactions. A comprehensive assessment of the potential risks associated with these drug interactions throughout the treatment process is extremely important **(Friton, *et al*., 2005; Jager *et al*., 2016).** Serum biochemical and coagulation markers can be used to assess the effects and potential toxicity of the drug in the body. Monitoring these markers can help to manage drug therapy appropriately by enabling early detection of potential side effects **(Lascelles, *et al*., 2005; Er, *et al*., 2013).** In this context, we investigated the effects of MBX and KTP after IM administration on the basis of biochemical and coagulation markers.

All groups had no significant statistical difference in their ALB and BUN values during the within-group evaluation in this research. It was determined that CK and LDH values increased significantly at the 24 hours compared to the 0 hour in the MBX and MBX+KTP groups. The transient increase in LDH and CK levels in the MBX and MBX+KTP groups may occur due to muscle damage caused by IM injection of MBX because LDH and CK levels did not increase in the KTP group. In the MBX group, the AST value increased significantly at the 24 hours compared to the 0 hour. In MBX+KTP groups, AST level increased insignificantly. Serum

AST and ALT levels can be used as an indicator of liver damage **(Sriuttha, *et al.*, 2018).** In earlier studies, it was reported that IM administration of MBX increased the AST enzyme in calves **(El-sayed, *et al.*, 2019)** and sheep **(Coşkun, *et al.*, 2019).** These results agree with finding of our study. In the KTP group, ALT, AST and CRE values decreased at the 24 hours compared to the 0 hour but increased again at the 48 hours. There was no statistically important difference in ALB, BUN and CRE values between the groups.

However, ALT, AST, CK and LDH values in the MBX and MBX+KTP groups at 24 hours was significantly higher than that in the KTP group. Although it is known that fluoroquinolones are well tolerated by the liver, it has been reported that they may cause transient moderate increases in liver function parameters **(Liu, *et al.*, 2017).** It has been reported that IV administration of KTP at a dose of 3 mg/kg for 5 alternate days in calves is well tolerated and does not lead to significant alterations in biochemical and hematological parameters **(Singh, *et al.*, 2009).** In our study, it was concluded that mild and transient fluctuations in serum enzyme levels are associated with the metabolism and elimination processes of MXB.

PT and aPTT are commonly used coagulation measurement parameters to evaluate the functioning and balance of the blood coagulation system in humans and animals **(Tripodi, *et al.*, 2009; Zanuzzo, *et al.*, 2015).** It is known that KTP causes bleeding tendency by disrupting platelet aggregation and prolongs bleeding time **(Stichtenoth, *et al.*, 1996).** The effects of fluoroquinolones on coagulation parameters may vary based on a variety of factors, including the patient's general health, dosage, and duration of treatment. In previous studies, they were reported that temafloxacin and ciprofloxacin did not cause a important difference in PT and aPTT values **(Mant, *et al.*, 1992; Ziemen *et al.*,1998).** In this study, it was concluded higher PT and aPTT values at 24 hours in the MBX+KTP and KTP groups compared to the MBX group were due to KTP injection.

Fibrinogen value increased in the MBX group at the 24 hours compared to the 0 hour, and decreased below the 0 hour value at the 48 hours. It was significantly decreased in MBX+KTP and KTP groups at 48 hour compared to 24 and 0 hour. Fibrinogen value at 48 hour was significantly different in all groups. It was highest in MBX group and lowest in KTP group. Fibrinogen is a plasma protein produced by the liver and plays a fundamental role in coagulation processes. It has been stated that NSAIDs can inhibit the release of some platelet-related substances such as fibrinogen in the venous circulation by inhibiting platelet aggregation **(Gunaydin and Bilge, 2018).** Here was no significant statistical variance in D-dimer values between the groups.. However, D-dimer levels increased significantly in the KTP group at the 24 hour compared to the 0 hour. These findings are consistent with the study that demonstrates that non-selective NSAID use causes an increase in D-dimer levels **(Allen, 2009).**

CONCLUSION

In this study, the effects of single and simultaneous IM injections of MBX and KTP on some biochemical and coagulation parameters were evaluated. It was observed that IM injection of MBX to calves increased CK and LDH values, which may be related to muscle damage. This may limit the administration via IM route of MBX to calves. In addition, it was determined that KTP increased the PT and aPTT values but decreased the fibrinogen value. As a result, it can be stated that in both alone MBX, and KTP administration and their combination, further studies are required to determine the safety of drugs after repeated administrations and other administration routes in calves.

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Conflicts of interest

The writers declare that there are no potential conflicts of interest related to the creation or dissemination of this article.

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