Slov Vet Res

DOI 10.26873/SVR-1725-2023
UDC 577:591.111.1:591.182:611.018.5:615.212:616-001:636.32/.38
Pages: 97–103

Original Research Article

The Effect of Ascending Doses of Ketoprofen on Biochemical and Coagulation Parameters in Lambs

Key words

drug safety;
haemostatic function;
hepatotoxicity;
ketoprofen;
lambs;
nephrotoxicity;
non-steroidal anti-inflammatory drug

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Abstract: Ketoprofen (KTP) is a non-steroidal anti-inflammatory drug (NSAID) used as an analgesic, antipyretic and anti-inflammatory agent in human and veterinary medicine. Although KTP is used in the treatment of diseases such as musculoskeletal inflammation, endotoxemia, pneumonia, enteritis in sheep and minor surgical procedures such as dehorning and castration there is no information about its safety. The aim of this study is to determine the effect of KTP on biochemical and coagulation parameters following intramuscular (IM) administration of different doses of KTP to lambs. In the study, 18 clinically healthy lambs were randomly divided into three groups of 6 animals each. KTP was administered IM to lambs at doses of 1.5, 3 and 6 mg/kg. Biochemical and coagulation parameters were evaluated by taking blood samples before drug administration (0 hour) and at 24 hours and 48 hours after administration. No local or systemic side effects were observed in lambs after the administration of KTP at different doses. The aspartate aminotransferase (AST), creatine kinase (CK) and lactate dehydrogenase (LDH) values at 24 hours significantly increased compared to 0 hours in all dosage groups ($p<0.05$). KTP did not cause a significant change in albumin (ALB), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine (CRE), CK and LDH values in different dose groups. The AST value was only significantly higher in the 6 mg/kg dose group compared to the 1.5 mg/kg dose group at 24 hours ($p<0.05$). Although there was no statistically significant difference in intragroup prothrombin time (PT), fibrinogen and D-dimer levels in all dose groups, a significant increase was observed in the activated partial thromboplastin time (aPTT) value of 6 mg/kg dose group at the 24 hours compared to the 0 hour ($p< 0.05$). As a result, after IM administration of 1.5, 3 and 6 mg/kg, increased CK and LDH values, which may be associated with muscle damage, may limit use of KTP via IM injection in lambs.

Received: 19 March 2023
Accepted: 6 July 2023

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), which are widely used in painful and inflammatory conditions such as lameness, foot rot, castration, vasectomy, mastitis and laparoscopy in sheep, act by inhibiting the effect of the cyclooxygenase enzyme, which is responsible for the synthesis of prostaglandins (1-3). Ketoprofen (KTP), is a NSAID belonging to the arylpropionic acid group and exists as a chiral compound with R(-) and S(-) isomers present in the racemic formulation. In animals, the S(-) form is more active and there is interconversion between the forms (4). In sheep, the suppression of prostaglandin E2 (PGE2) and thromboxane B2 (TXB2) production has been reported for up to 12 hours following a single intravenous injection of 1.5 or 3 mg/kg of KTP (5). In addition, a study in sheep reported that the 4 mg/kg subcutaneous administration of KTP at 90 minutes before the procedure failed to alleviate the post-surgical pain response (6).

It is known that NSAID therapy has serious side effects such as gastrointestinal ulceration or bleeding, liver and

kidney damage, allergic reactions, myocardial infarction and cardiac sudden death. Coagulation, hematological and biochemical parameters are used to evaluate the effects of drugs on physiological and pathological conditions (7,8). Coagulation parameters (aPTT, PT, fibrinojen, D-dimer) reflect coagulation disorders, while hematological parameters (WBC, RBC, hemogram, hematocrit, platelet) reflect bone marrow functions and fluid electrolyte balance, biochemical parameters (albumin, ALP, ALT, AST, BUN, cholesterol, CK, creatinine, GGT, TP and triglyceride) reflect liver, kidney, muscle and lipid metabolism functions (9,10).

In studies conducted in calves, horses, dogs, pig and children, it has been shown that the administration of KTP at recommended doses does not cause any side effects (11-15). On the other hand, some studies in laboratory animals have reported that KTP administered at recommended therapeutic doses causes side effects such as gastrointestinal irritation, impaired kidney function, hepatopathies, prolonged bleeding and clotting times (13,16). In some cases, NSAIDs may need to be used in high doses. However, high doses of this group of drugs may cause undesirable effects. In the literature review, no reference was found regarding the effect of increasing doses of KTP on biochemical and coagulation parameters in lambs. The aim of this study was to determine the effects of KTP on biochemical and coagulation parameters after single doses of 1.5, 3 and 6 mg/kg in lambs.

Material and Methods

Animals

The study was performed on a commercial farm located in the district of Kadınhanı, Konya Province, Türkiye. The study was performed on 18 female Akkaraman lambs (3-6 months old, 23-36 kg) who were determined to be healthy in the general clinical examination and had not received any medication treatment in the one months prior to the study. The animals were divided into different groups 7 days before the start of the study and numbered with oily paint. The lambs were fed with commercial feed (CP-5621, Ankara, Türkiye) twice a day and alfalfa hay, grass hay and water were given ad libitum. All procedures on animals were approved of the Local Ethics Committee for Animal Experiments at Selcuk University on December 27, 2022 with the approval number 2022/140.

Experimental design

A total of 18 lambs were randomly divided into three groups of 6 animals each. KTP (100 mg/ml, Ba-Keto, Injection Solution, Bavet, Turkey) was administered as a single dose via intramuscular injection into the neck region of the lambs in the first, second and third groups at doses of 1.5 mg/kg, 3 mg/kg and 6 mg/kg, respectively, following the dosage references from previous studies (5,6). In the study, blood samples were collected from the jugular vein at 0, 24 and 48 hours using a venipuncture technique. Blood samples were collected into gel tubes (2 ml) for biochemical analysis and into sodium citrate tubes (2 ml) for coagulation tests. After centrifuging the blood samples at 3,500g for 10 minutes, the resulting serum and plasma samples were carefully transferred into 2 ml Eppendorf tubes. The serum samples were stored in a deep freezer at -80°C until the day of analysis, while the plasma samples were analyzed within 3 hours for coagulation tests. Throughout the experimental protocol, the injection site was monitored for swelling, redness and pain and the animals were closely observed for any clinical changes.

Analysis of biochemical parameters

Biochemical parameters including serum albumin (ALB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatine kinase (CK), creatinine (CRE) and lactate dehydrogenase (LDH) levels were determined using an automated analyzer device (Lab-300plus, Instrumentation Laboratory, Milano, Italy) from serum samples stored at -80°C.

Analysis of coagulation parameters

In plasma samples, the measurement of clotting factors including prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen (FIB) and D-Dimer was performed using a coagulation analysis device (Siemens, A-7799, Sysmex CA 1500, Germany).

Statistical analysis

The research data was 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 lambs following intramuscular administration of KTP at doses of 1.5, 3 and 6 mg/kg.

The effect of KTP on the biochemical parameters of lambs after intramuscular administration at doses of 1.5, 3 and 6 mg/kg is presented in Table 1. In the evaluation within the group, there was no statistically significant difference in

Table 1: The effects on biochemical parameters of intramuscular administration of ketoprofen at doses of 1.5, 3 and 6 mg/kg to lambs (n=6, mean ± SD)

Parameters	Sampling Time (Hour)	1.5 mg/kg	3 mg/kg	6 mg/kg
ALB (g/L)	0	29.83±5.91	33.25±3.03	32.58±4.34
	24	34.25±1.72	35.33±3.33	34.42±2.73
	48	33.66±1.63	35.08±6.74	33.33±3.63
ALT (U/L)	0	16.08±3.64	19.17±3.60	17.92±4.76
	24	19.67±6.22	22.75±7.44	24.08±6.59
	48	18.33±4.89	15.50±5.00	19.33±1.08
AST (U/L)	0	97.25 ± 16.67^{y}	104.00 ± 12.15^{y}	97.17 ± 6.35^{z}
	24	$147.17\pm10.44^{b,x}$	$164.08\pm12.71^{ab,x}$	$180.33\pm13.85^{a,x}$
	48	115.42 ± 13.25^{y}	121.33 ± 29.44^{y}	124.58 ± 20.31^{y}
BUN (mg/dL)	0	72.08±6.71	73.33±9.01	73.75±6.05
	24	75.58±7.79	70.25±7.11	70.92±8.79
	48	70.58±6.33	71.58±5.39	70.25±7.24
CRE (mg/dL)	0	0.65±0.04	0.64±0.06	0.68±0.04
	24	0.79±0.18	0.76±0.16	0.71±0.13
	48	0.72±0.14	0.61±0.14	0.72±0.15
CK (U/L)	0	223.75 ± 22.94^{y}	243.58 ± 11.00^{y}	231.33 ± 41.68^{y}
	24	399.25 ± 73.72^{x}	384.42 ± 38.51^{x}	426.33 ± 145.25^{x}
	48	252.67 ± 35.07^{y}	268.25 ± 16.58^{y}	285.92 ± 55.26^{y}
LDH (U/L)	0	620.00 ± 47.18^{y}	640.92 ± 35.72^{y}	629.92 ± 47.10^{y}
	24	891.50 ± 128.45^{x}	880.25 ± 152.23^{x}	877.58 ± 153.09^{x}
	48	827.00 ± 81.93^{x}	830.50 ± 113.06^{x}	818.08 ± 140.62^{x}

^{a,b} Superscripts with different letter in the same raw show statistically significant differences ($P < 0.05$). ^{x,y,z} Superscripts with different letter in the same column show statistically significant differences ($P < 0.05$).

ALB; Albümin, AST; aspartate aminotransferase, ALT; alanine aminotransferase, BUN; blood urea nitrogen, CRE; Creatinine, CK; creatine kinase and LDH; lactate dehydrogenase.

ALB, ALT, CRE and BUN values in all dose groups ($p>0.05$). However, the AST, CK and LDH values at 1.5, 3 and 6 mg/kg doses increased at 24 hours compared to 0 hour ($P<0.05$). The AST and CK values at 1.5, 3 and 6 mg/kg doses decreased at 48 hours compared to 24 hours ($P<0.05$). There was no statistically significant difference in ALB, ALT, BUN, CRE, CK and LDH values between the groups ($P>0.05$). However, AST value in the 6 mg/kg dose group at 24 hours was significantly higher than that in the 1.5 mg/kg dose group ($P<0.05$).

The effect of KTP on coagulation parameters in lambs at doses of 1.5, 3 and 6 mg/kg after intramuscular administration is presented in Table 2. In the within-group evaluation, there was no statistically significant difference in PT and D-Dimer values in all dose groups ($P>0.05$). However, the aPTT value increased significantly at 6 mg/kg at 48 hours compared to 0 hours ($P<0.05$). In the evaluation between groups, there was no statistically significant difference in PT and D-Dimer values ($P>0.05$). However, the aPTT value in the 3 mg/kg dose group was significantly lower at 48 hours compared to the value in the 1.5 mg/kg dose group

Table 2: The effects on coagulation parameters of intramuscular administration of ketoprofen at doses of 1.5, 3 and 6 mg/kg to lambs (mean ± SD)

Parameters	Sampling Time (Hour)	1.5 mg/kg	3 mg/kg	6 mg/kg
PT (sn)	0	12.80±0.47	13.42±1.13	13.22±1.28
	24	14.65±2.32	13.55±1.15	12.87±1.03
	48	12.75±0.66	12.70±0.74	13.42±1.01
aPTT (sn)	0	38.17±0.83	36.47±2.46	37.28±2.04^{y}
	24	39.30±1.87	35.85±1.20	40.53±7.21^{xy}
	48	40.75±3.03^{a}	35.62±3.15^{b}	44.40±1.75^{a,x}
Fibrinogen (g/L)	0	2.21±0.17	1.88±0.25	1.96±0.28
	24	1.53±0.56^{b}	2.35±0.50^{a}	1.60±0.55^{ab}
	48	1.98±1.05	2.41±0.56	2.41±0.75
D-DIMER (ng/L)	0	457.67±64.97	501.83±85.35	535.83±51.57
	24	551.00±57.84	487.33±104.93	501.33±114.63
	48	524.67±82.46	518.50±62.91	512.00±63.22

^{a,b} Superscripts with different letter in the same raw show statistically significant differences (P < 0.05). ^{x,y} Superscripts with different letter in the same column show statistically significant differences (P < 0.05). PT; prothrombin time, aPTT; activated partial thromboplastin time

and the fibrinogen value in the 3 mg/kg dose group was significantly higher at 24 hours compared to the value in the 1.5 mg/kg dose group (P<0.05).

Discussion

KTP, a widely used NSAID in humans and animals, is a potent cyclooxygenase inhibitor. Unlike other NSAIDs, it also inhibits lipoxygenase and creates a double blockade in arachidonic acid metabolism. The recommended dose of KTP is 2 mg/kg for cats and dogs, 2.2 mg/kg for horses and 3 mg/kg for cattle and small ruminants (4,16). Since the effect of KTP varies depending on the dose, it can be applied in increasing doses (17,18), but undesirable effects may occur when used in increasing doses. The doses (1.5, 3 and 6 mg/kg) selected in this study and sample collection times were determined by considering previous studies in pigs, sheep and cattle (5,19,20). Common side effects of KTP are observed when it is used at higher doses than recommended or for a prolonged period of time. However, side effects are rarely reported after a single administration at the recommended dose (21). KTP administered intravenously at a dose of 3 mg/kg for 5 days was well tolerated in calves (11).

It has been found that gastrointestinal side effects tend to occur when dogs are given KTP for 30 days, but the lesions healed after administration have been discontinued (13). Horses did not show any clinical adverse effects during administration of 2.2 mg/kg three times daily KTP (12). Oral administration of KTP in children has been reported to be well tolerated for up to three weeks (15). In pigs, there was no change in serum biochemical values at the single intramuscular dose of 3, 6 and 9 mg/kg and 3 mg/kg for 3 days (14). In this study, no side effects were observed after IM administration of 1.5, 3 and 6 mg/kg KTP to lambs, but statistically significant intra and intergroup differences were observed in some biochemical and coagulation parameters. Most of the reports on the side effects of KTP administered at recommended treatment doses are obtained from humans and laboratory animals. These effects include gastrointestinal irritation, impaired kidney function, hepatopathies, prolonged bleeding and clotting times and photosensitivity (10,14). Gastrointestinal ulceration occurs due to inhibition of PGE2 synthesis and decreased production of mucosal protective agents (22). Nephrotoxicity is related to the inhibition of prostaglandins in the kidneys that are essential for salt and water balance, vascular tone, blood flow and renin secretion (23). Coagulation disorders are the result of thromboxane A2 deficiency in platelets after administration of COX1 inhibitors (24). Phototoxicity results from damage to cell membranes by radical intermediates (25).

In this study, AST, CK and LDH values increased at 24 hours compared to 0 hours in all dose groups (P<0.05). It was observed that AST and CK values decreased (P<0.05) in 48 hours compared to 24 hours, but LDH value did not change. The increase in serum CK and LDH levels may occur due to muscle damage caused by IM drug administration (26,27).

The halflife of CK is approximately 2 hours (28), thus indicating that the transient increase in serum CK level seen in this study is due to IM drug administration. In our study, it was concluded that mild and transient increases in enzyme levels, particularly within the same dosage groups, are related to the metabolism and elimination processes of KPT. In the current study, it was determined that KTP did not cause a significant change in ALB, ALT, BUN, CRE, CK and LDH values in different dose groups. Only the AST value in the 6 mg/kg dose group was significantly higher at the 24 hours compared to the 1.5 mg/kg dose group ($p<0.05$). It was determined that the elevated AST level returned to its normal levels in the 48 hours. AST also known as serum glutamate-oxaloacetate transaminase (SGOT), is found mainly in the heart, liver, kidneys and muscle tissue and high blood concentrations indicate liver damage or disease (29). Serum AST and ALT levels can be used as an indicator of liver damage. ALT is more liver specific than AST. AST instead of ALT can only be used when ALT is not present and there is no known muscle pathology causing an increase in AST (30). In previous studies, it was reported that KTP administration increased the AST enzyme in mice (31), dogs (32) and donkeys (33). These results are consistent with the results of our study. Low elevations in serum enzyme levels have been reported during KTP therapy and this has rarely been associated with significant acute liver injury (31).

KTP blocks the formation of thromboxane A2 by inhibiting thromboxane cyclooxygenase. It creates a systemic bleeding tendency by disrupting platelet aggregation and thus prolonging bleeding time (34, 35). In this study, although no statistically significant difference was found in intragroup PT, fibrinogen and D-dimer levels in all dose groups, a significant increase was observed in aPTT value at 6 mg/kg in 24 hours compared to 0 hour ($p<0.05$). PT and aPTT are commonly used coagulation measurement parameters in the evaluation of secondary hemostasis in humans and animals (36). aPTT level in healthy sheep has been reported to be between 29.2 ± 3.2 and 41.1 ± 8.7 seconds (37). It was reported that the administration of flunixin meglumine and meloxicam in sheep prolonged aPTT, but these changes were not statistically significant (38). It has been determined that carprofen increased the aPTT value in dogs on the 5, 7 and 12 days after administration (36). It has been reported that the administration of meloxicam and KTP in ponies did not cause any difference in fibrinogen, PLT, PT and aPTT values and did not affect the coagulation parameters (39). In this study, it was concluded that the fact that the fibrinogen value in the 3 mg/kg dose group was higher at 24 hours compared to the value in the 1.5 mg/kg dose group was not significant.

Conclusion

In conclusion, after IM administration of 1.5, 3 and 6 mg/kg of KTP, it was observed that CK and LDH values, which may be associated with muscle damage, were increased. This may limit use of KTP via IM route in lambs. In all dose groups, AST values, which may be associated with metabolism processes of KTP, were increased. The aPTT value increased at the dose of 6 mg/kg. For the effective and safe use of KTP in lambs, its hematological, biochemical, molecular and pathological safety must be demonstrated after repeated administrations and other administration routes.

Acknowledgements

The authors would like to express their gratitude to the people working on the farm where the experimental procedure on the lambs took place.

Conflict of interest: The authors declare that they have no potential conflict of interest with respect to the authorship and/or publication of this article.

References

1. Curry SL, Cogar SM, Cook JL. Nonsteroidal antiinflammatory drugs: a review J Am Anim Hosp Assoc 2005; 41(5): 298–309.
2. Ricciotti E, FitzGerald GA. Prostaglandins and inflammation. Arterioscler Thromb Vasc Biol 2011; 31(5): 986–1000.
3. Lizarraga I, Chambers JP. Use of analgesic drugs for pain management in sheep. N Z Vet J 2012; 60(2): 87–94.
4. Papich MG. Papich handbook of veterinary drugs. 5th ed. Philadelphia: Elsevier Saunders, 2021: 498–500.
5. Arifah AK, Landoni MF, Frean SP, Lees P. Pharmacodynamics and pharmacokinetics of ketoprofen enantiomers in sheep. Am J Vet Res 2001; 62(1): 77–86.
6. Paull DR, Colditz IG, Lee C, Atkinson SJ, Fisher AD. Effectiveness of non-steroidal anti-inflammatory drugs and epidural anaesthesia in reducing the pain and stress responses to a surgical husbandry procedure (mulesing) in sheep. Aust J Exp Agric 2008; 48: 1034–1039.
7. Er A, Dik B, Corum O, et al. Cardiac safety of diclofenac at a single dose in ram. ScientificWorldJournal 2013: 808731. doi: 10.1155/2013/808731
8. Lascelles BDX, McFarland JM, Swann H. Guidelines for safe and effective use of NSAIDs in dogs. Vet Ther 2005; 6(3): 237–51.
9. Çorum O, Uney K, Er A, Durna Corum D. The effect of cefquinome on hematological and biochemical parameters following repeated subcutaneous administrations in sheep. Vet J Kastamonu Univ 2022; 1(1): 1–7.
10. Herring J, McMichael M. Diagnostic approach to small animal bleeding disorders. Top Companion Anim Med 2012; 27(2): 73–80.
11. Singh RD, Devi S, Gondaliya SR, Bhavsar SK, Thaker AM. Safety of Ketoprofen in Cow calves following repeated intravenous administration. Vet World 2009; 2(3): 105–7.
12. MacAllister CG, Morgan SJ, Borne AT, Pollet RA Comparison of adverse effects of phenylbutazone, flunixin meglumine, and ketoprofen in horses. J Am Vet Med Assoc 1993; 202(1): 71–7.
13. Narita T, Tomizawa N, Sato R, Goryo M, Hara S. Effects of long-term oral administration of ketoprofen in clinically healthy beagle dogs. J Vet Med Sci 2005; 67(9): 847–53.

14. Fazzio LE, Raggio SJ, Romero JF, MembrebeJ, Minervino AHH. Safety study on ketoprofen in pigs: evaluating the effects of different dosing and treatment scheme on hematological, hepatic, and renal parameters. Vet Sci 2021; 8(2): 30. doi: 10.3390/vetsci8020030

15. Kokki H. Ketoprofen pharmacokinetics, efficacy, and tolerability in pediatric patients. Pediatr Drugs 2010; 12(5): 313–29.

16. Luna SP, Basílio AC, Steagall PV, et al. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. Am J Vet Res 2007; 68(3):258–64.

17. Spofford CM, Ashmawi H, Subieta A, et al. Ketoprofen produces modality-specific inhibition of pain behaviors in rats after plantar incision. Anesth Analg 2009; 109(6):1992–9.

18. Prado WA, Pontes RMC. Presurgical ketoprofen, but not morphine, dipyrone, diclofenac or tenoxicam, preempts post-incisional mechanical allodynia in rats. Braz J Med Biol Res 2002; 35: 111–9.

19. Salichs M, Sabaté D, Ciervo O, Homedes J. Comparison of the antipyretic efficacy of ketoprofen, acetylsalicylic acid, and paracetamol, orally administered to swine. J Vet Pharmacol Ther 2012; 35(2): 198–201.

20. De Koster J, Boucher JF, Tena JK, Gehring R, Stegemann MR. Co-formulation of ketoprofen with tulathromycin alters pharmacokinetic and pharmacodynamic profile of ketoprofen in cattle. J Vet Pharmacol Ther 2022; 45(1): 69–82.

21. Lamon TK, Browder EJ, Sohrabji F, Ihrig M. Adverse effects of incorporating ketoprofen into established rodent studies. J Am Assoc Lab Anim Sci 2008; 47(4): 20–4.

22. Lascelles BDX, Court MH, Hardie EM, Robertson SA. Nonsteroidal anti-inflammatory drugs in cats: a review. Vet Anaesth Analg 2007; 34(4): 228–50.

23. Cheng HF, Harris RC. Renal effects of non-steroidal anti-inflammatory drugs and selective cyclooxygenase-2 inhibitors. Curr Pharm Des 2005; 11(14): 1795–804.

24. Krötz F, Schiele TM, Klauss V, Sohn HY. Selective COX-2 inhibitors and risk of myocardial infarction. J Vasc Res 2005; 42(4): 312–24.

25. Jenerowicz D, Jakubowicz O, Polańska A, Przytocka SA, Pazdrowska AD, Żaba R. Review paper Photosensitivity to selected topical nonsteroidal anti-inflammatory drugs preparations–a review of literature data and author's own experience. Cent Eur J Immunol 2011; 36(3): 197–203..

26. Narjes H, Türck D, Busch U, Heinzel G, Nehmiz G. Pharmacokinetics and tolerability of meloxicam after im administration. Br J Clin Pharmacol 1996; 41(2):135–9.

27. Klein R, Nagy O, Tóthová C, Chovanová F. Clinical and diagnostic significance of lactate dehydrogenase and its isoenzymes in animals. Vet Med Int 2020; 2020: 5346483. doi: 10.1155/2020/5346483

28. Smith GS, Walter GL, Walker RM. Clinical pathology in non-clinical toxicology testing. In: Haschek WM, Rousseaux CG, Wallig MA, eds. Haschek and Rousseaux's handbook of toxicologic pathology. Amsterdam: Academic Press, 2013: 565–94.

29. Ndrepepa G. Aspartate aminotransferase and cardiovascular disease—a narrative review. J Lab Precis Med 2021; 6: 6. doi: 10.21037/jlpm-20-9

30. Sriuttha P, Sirichanchuen B, Permsuwan U. Hepatotoxicity of nonsteroidal antiinflammatory drugs: a systematic review of randomized controlled trials. Int J Hepatol 2018; 2018: 5253626. doi: 10.1155/2018/5253623

31. Paunescu A, Ponepal CM, Zagardan MC, et al. Evaluation of histophysiological alterations associated with ketoprofen administration in albino NMRI mice. Naunyn Schmiedebergs Arch Pharmacol 2020; 393(6): 1033–9.

32. Ugwu N, Eze C, Udegbunam R. Evaluation of haematological and serum biochemical changes associated with constant rate infusion tramadol hydrochloride as an adjunct to ketoprofen in laparotomized and ovariohysterectomized dogs. Comp Clin Path 2017; 26: 1135–40.

33. Mozaffari AA, Derakhshanfar A, Alinejad A, Moorovati M. A comparative study on the adverse effects of flunixin, ketoprofen and phenylbutazone in miniature donkeys: haematological, biochemical and pathological findings. N Z Vet J 2010; 58(5): 224–8.

34. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. J Clin Pharmacol 1995; 35(3): 209–19.

35. Stichtenoth DO, Tsikas D, Gutzki FM, Frölich JC. Effects of ketoprofen and ibuprofen on platelet aggregation and prostanoid formation in man. Eur J Clin Pharmacol 1996; 51(3/4): 231–4.

36. Zanuzzo FS, Teixeira-Neto FJ, Thomazini CM, Takahira RK, Conner B, Diniz MS. Effects of dipyrone, meloxicam, or the combination on hemostasis in conscious dogs. J Vet Emerg Crit Care (San Antonio) 2015; 25(4): 512–20.

37. Foley SR, Solano C, Simonova G, et al. A comprehensive study of ovine haemostasis to assess suitability to model human coagulation. Thromb Res 2014; 134(2): 468–73.

38. Turgut S, Parlatır Y, Erdoğan H, Paşa S. Investigation of the effects of flunixine meglumine and meloxycam administration on coagulation profiles in healthy sheep. Ataturk Univ J Vet Sci 2018;13(3): 301–8.

39. Pozzobon R, Brass KE, Rubin MIB, et al. Meloxicam and ketoprofen did not alter coagulation and haematological parameters of healthy ponies.In: Proceedings of the 11th International Congress of World Equine Veterinary Association, Guarujá: WEVA, 2009. https://www.ivis.org/library/weva/weva-internal-congress-brazil-2009/meloxicam-and-ketoprofen-did-not-alter-coagulation (20. 1. 2023)

Vpliv naraščajočih odmerkov ketoprofena na biokemične in koagulacijske parametre pri jagnjetih

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Izvleček: Ketoprofen (KTP) je nesteroidno protivnetno zdravilo (NSAID), ki se v humani in veterinarski medicini uporablja kot sredstvo proti bolečinam, povišani temperaturi in vnetju. Čeprav se KTP pri ovcah uporablja za zdravljenje mišično-skeletnih vnetij, endotoksemije, pljučnice, enteritisa in pri manjših kirurških posegih, kot sta odstranjevanje rogov in kastracija, ni podatkov o varnosti zdravila. Namen te študije je bil ugotoviti vpliv biokemijskih in koagulacijskih parametrov po intramuskularni (IM) aplikaciji različnih odmerkov KTP pri jagnjetih. Vrednosti aspartataminotransferaze (AST), kreatin kinaze (CK) in laktat dehidrogenaze (LDH) so se po 24 urah v primerjavi z 0 urami v vseh skupinah znatno povečale ($p < 0,05$). KTP ni povzročil značilnih sprememb vrednosti albumina (ALB), alanin aminotransferaze (ALT), dušika sečnine v krvi (BUN), kreatinina (CRE), CK in LDH v različnih skupinah odmerkov. Vrednost AST je bila po 24 urah pomembno višja le v skupini z odmerkom 6 mg/kg v primerjavi s skupino z odmerkom 1,5 mg/kg ($p < 0,05$). Čeprav znotraj posameznih skupin ni bilo statistično pomembnih razlik v vrednostih protrombinskega časa (PT), fibrinogena in D-dimerov, smo v skupini z odmerkom 6 mg/kg v 24 urah v primerjavi z uro 0 opazili znatno povečanje vrednosti aktiviranega delnega tromboplastinskega časa (aPTT) ($p < 0,05$). Posledično bi lahko povečane vrednosti CK in LDH (ki so lahko povezane s poškodbami mišic) omejile uporabo IM aplikacije KTP pri jagnjetih.

Ključne besede: varnost zdravil; hemostatska funkcija; hepatotoksičnost; ketoprofen; jagnjeta; nefrotoksičnost; nesteroidno protivnetno zdravilo