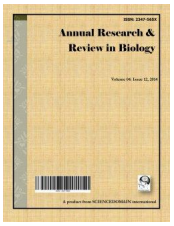

Annual Research & Review in Biology

29(6): 1-8, 2018; Article no.ARRB.45152
ISSN: 2347-565X, NLM ID: 101632869

Are COX-2 Selective NSAIDs Associated with Less GI, Renal, and Cardiovascular Side Effects: Evidence from Animals Treated with NSAIDs

Suong N. T. Ngo[1*] and Caitlin J. Addison[1]

[1]School of Animal and Veterinary Sciences, The University of Adelaide, Roseworthy, SA 5371, Australia.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ARRB/2018/45152
Editor(s):
(1) Dr. George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Fulya Ustun Alkan, Istanbul University, Turkey.
(2) C. Thangam, K.S.R Institute of Dental sciences and Research Tiruchengode, India.
(3) Sergio Parco, University of Trieste, Italy.
Complete Peer review History: http://www.sciencedomain.org/review-history/27839

Review Article

Received 11 September 2018
Accepted 26 November 2018
Published 18 December 2018

ABSTRACT

Aims: Nonsteroidal anti-inflammatory drugs (NSAIDs) are frequently used to treat both acute and chronic pain in animals, especially when the pain is resulted from inflammatory conditions. NSAIDs work by inhibition of cyclooxygenases (COX) enzymes and reduce the production of key inflammatory mediators prostaglandins and associated chemicals. Prostaglandins have important roles in pain signalling and haemostasis, including platelet aggregation and gastric mucosal protection. There are two known isoforms of cyclooxygenases enzymes, namely COX-1 and COX-2. Notable adverse effects commonly resulted from NSAIDs uses include gastrointestinal ulceration, compromised haemostasis and renal toxicity, which are due to inhibition of COX-1 isoform. Despite the development of COX-2 selective medicines and continuing effort to improve the safety of NSAIDs in routine veterinary practice, adverse effects of NSAIDs still exist and require closed monitoring. This study aims to summarise and evaluate the current literature on reported adverse effects of NSAIDs used in animals and to compare COX-2 selective versus non-selective agents.

Methodology: Literature on reported adverse effects of NSAIDs used in animals over the last

**Corresponding author: E-mail: suong.ngo@adelaide.edu.au;*

decade has been systematically reviewed. Some older sources from the primary literature search have also been included to determine the background information leading to current rationale behind NSAIDs' therapeutic uses, dosage and route of administration, observed adverse effects and COX-2 selective versus non-selective agents. The primary focus of this study is NSAIDs administered to animals in prospective randomised placebo-controlled blinded trials.

Results: A total of 12 studies that met the inclusion criteria were included in the review, with total 13 NSAIDs being discussed, including meloxicam, phenylbutazone, deracoxib, carprofen, aspirin, firocoxib, vedaprofen, etorolac, ketoprofen, tepoxalin, rofecoxib, licofelone and flunixin. It was found that there were variable findings in comparing the adverse effects associated with COX-2 selective NSAIDs and non-selective NSAIDs. COX-2 selective NSAIDs have been found associated with no adverse effects in some studies and minimal adverse effects in other studies. Severe adverse effects were reported for COX-2 selective NSAID administered at higher than recommended doses or for a long duration and some studies reported reduced adverse effects in COX-2 selective NSAIDs when compared to non-selective NSAIDs. Overall, gastrointestinal adverse effects were predominantly reported, followed by adverse findings relating to haemostasis and renal function.

Conclusion: Collectively, the findings suggest COX-2 selective NSAIDs provide a clinically useful improvement over non-selective NSAIDs as well as reduce adverse effects when given at recommended dose.

Keywords: Adverse effect; NSAID; anti-inflammatory medicines; COX-2 selective.

1. INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are extensively used analgesics in current veterinary medicine in the treatment of acute pain, such as post-operative pain, as well as treatment of chronic pain and inflammatory conditions such as osteoarthritis. There is widespread acceptance that the mechanism of action of NSAIDs is via inhibition of cyclooxygenase (COX) enzymes, of which two main isoforms have been identified, namely COX-1 and COX-2. A splice isoform of COX-1 also exists, which is known as COX-3. Inhibition of these COX-1 and COX-2 enzymes results in decreased production of prostaglandins, which are key signalling chemical passengers involved in inflammation and pain pathway. Adverse effects of NSAIDs include but not limited to renal, hepatic, and coagulation disorders that are generally associated with the inhibition of COX-1 enzyme, as COX-1 is a house-keeping gene expressed constitutively and plays important role in various homeostatic processes [1,2].

NSAIDs can also be associated with inhibition of both COX-1/2 isoforms at different levels. The more recently developed COX-2 selective NSAIDs are proposed to be associated with reduced adverse effects compared to non-COX selective NSAIDs by maintaining constitutive COX-1 activity (COX-1-sparing effect). However, this COX-2 selective association with reduced adverse effects has not been proved in veterinary medicine, thus there is conflicting literature particularly regarding the production of gastrointestinal adverse effects with COX-2 selective NSAIDs admission in veterinary medicine [3,4]. Adverse effects associated with the administration of NSAIDs in veterinary clinical practice are of a high level of clinical relevance and importance due to the extensive use of these drugs in veterinary practice. The aim of this systematic review was to identify and compare the incidence of adverse-related effects between COX-2 selective NSAIDs and non-selective NSAIDs administered to animals in randomised placebo-controlled blinded studies.

2. MATERIALS AND METHODS

2.1 Data Source

An initial screening of the literature databases, including ISI Web of Science, Scopus, and PUBMED, was performed. The key search terms include, but are not limited to veterinary, NSAID, non-steroidal anti-inflammatory drugs, COX, cyclooxygenase, COX-2 selective, side effect, and adverse drug reaction. Following this initial search, a secondary screening was conducted based on the titles, abstracts and availability of full text to eliminate duplicates and irrelevant studies. Additionally, reference lists from review articles on the use of NSAIDs in veterinary medicine were assessed for relevant citations.

2.2 Selection Criteria

Selection criteria include: study published in English, primary blinded randomized controlled trial (RCT) of animal patients, field-based and/or

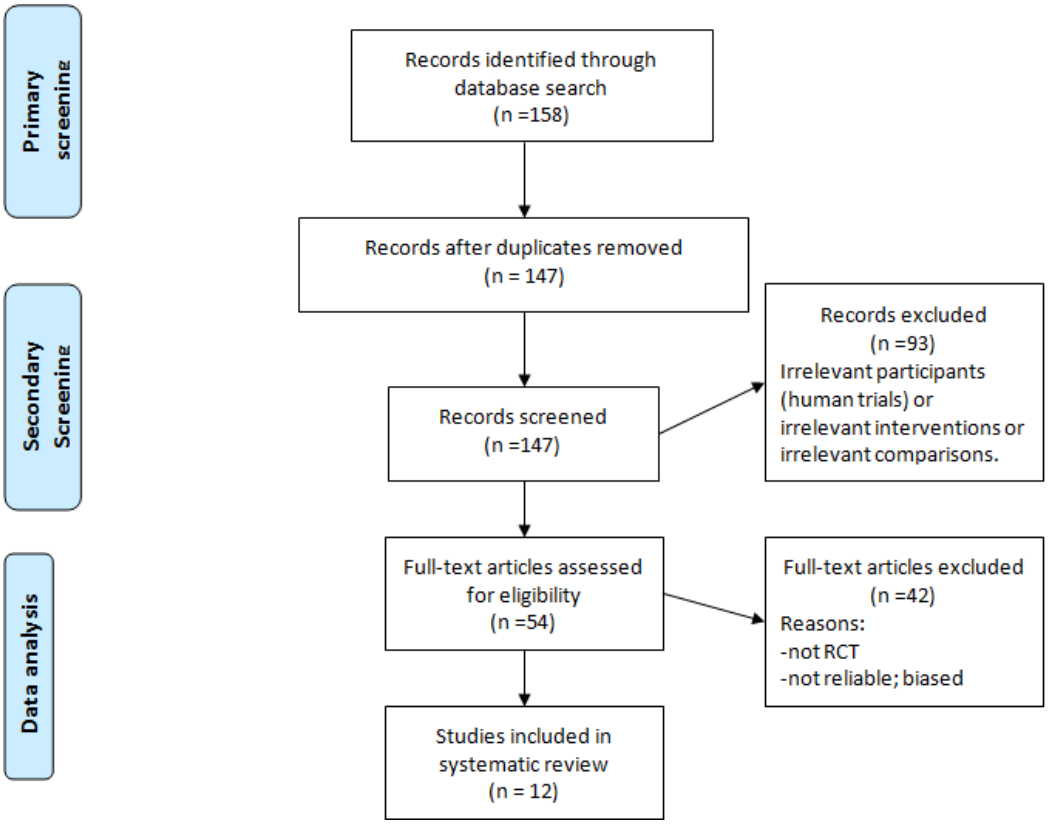

Fig. 1. Flowchart of the study selection and inclusion process

Adapted from Moher D, Liberati A, Altman DG et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7): e1000097 [5]

laboratory-based trials, study examined animal participants only, including dogs, cats, and horses, study compared the side effects of COX-2 selective NSAID to non-selective agents. As this review is concerning veterinary use of NSAIDs, only studies involving NSAIDs that are currently used in veterinary medicine as the intervention were included. NSAIDs used in veterinary medicine currently include, but are not limited to phenylbutazone, aspirin, carprofen, deracoxib and meloxicam.

Additionally, studies evaluated the efficacy and/or analgesic properties of NSAIDs without mention of adverse effects, or those evaluated the administration of NSAIDs in association with other drugs or involved NSAIDs formulated for human medicine or human patients, as well as cohort studies, case series, case reports, cross sectional studies were excluded. Literature that was deemed unreliable or heavily biased by the reviewers may also be subsequently excluded from the review. Two reviewers carried out the literature searching and evaluation, studies inclusion, and quality assessment. The main criteria that were used for quality assessment include, but are not limited to study's methodological quality, likelihood of random errors, blinding, and appropriate sample size of the study. Only studies that were considered of acceptable quality by both reviewers are included in the review. A flowchart of the study selection process and clinical data inclusion is provided in Fig. 1.

3. RESULTS

The literature search conducted for this review resulted in a total of 12 studies that met the inclusion criteria, with total 13 NSAIDs being discussed. The included NSAIDs were meloxicam, phenylbutazone, deracoxib, carprofen, aspirin, firocoxib, vedaprofen, etorolac, ketoprofen, tepoxalin, rofecoxib, licofelone and flunixin. Overall, one study investigated non-selective NSAIDs, six studies investigated

COX-2 selective NSAIDs, and five studies investigated both non-selective and COX-2 selective NSAIDs. Two of the 12 studies had horses as subjects and the remaining 10 studies had dogs as subjects. Population numbers of the included studies ranged from 8 to 60 subjects. Four of the 12 included studies were of crossover design and the remaining 8 had parallel methodology. Of the 12 identified studies, three studies involved a single NSAID intervention, with deracoxib investigated in two studies and meloxicam examined in one study. The remaining 9 studies involved comparisons of two or more NSAID treatments. Details of the reported side effects from the identified 12 studies are summarised in Table 1.

Overall, five studies addressed specifically adverse effects involving the gastrointestinal system observed in horse participants in two studies [6,7] and in dog participants in three studies [8-10]. Five studies investigated dose related adverse effects and/or long-term adverse effects of NSAID administration in dogs or horses [6,11-14]. One study investigated functional efficacy and adverse effects of NSAIDs in a sodium urate crystal induced synovitis model of canine osteoarthritis [15]. Also one study investigated the effects of NSAIDs on haemostatic mechanisms of dogs [16] and another study investigated specifically the adverse effects involving the kidneys and liver of NSAID admission in dogs [14]. Of the 12 studies included in this review, nine were classified as high quality and the remaining three were of moderate quality. Two reviews were involved in literature searching, ranking and study selection. Only studies which were considered of acceptable quality and meeting the inclusion criteria by both reviewers were included in the review.

Findings of outwardly detectable adverse effects in subjects treated with non-selective NSAIDs were reported in 2 studies and included preputial edema and melena. In subjects treated with COX-2 selective NSAID, outwardly detected adverse effects were reported in 2 studies and included vomiting, ventral edema, loose faeces and inappetance. Overall, adverse effects regarding gastrointestinal function were reported in seven studies. Gastrointestinal adverse effects in relation to admission of non-selective NSAIDs included gastric mucosal ulceration [6,13], right dorsal colitis [6,11], decreased right dorsal colon blood flow [7], occult blood in faeces [13], increased equine serum sucrose concentration measured via sucrose permeability testing (indicating decreased gastric mucosal integrity) [6] and hypoalbuminaemia [7]. Gastrointestinal related adverse effects associated with COX-2 selective NSAIDs only included gastric mucosal ulceration [10], however with higher than recommended dosage of COX-2 inhibitor administration the following adverse effects were also reported including right dorsal colitis [6], occult blood in faeces [13], gastric mucosal ulceration [6,11,13], decreased total serum protein and albumin concentrations [11], and hypoalbuminemia with long term administration of recommended dosage [14].

Adverse effects in relation to the renal system were reported in one study where histopathology revealed degeneration and regeneration in deracoxib treated dogs at 6 mg/kg/day. Fibrosis was noted in a few animals at 4 mg/kg/day and papillary necrosis was reported in four animals at 8 mg/kg/day [12]. In a study involving 10 dogs, significant decreased platelet aggregation ($P = .03$) was reported for COX-2 selective NSAID deracoxib whereby maximal platelet aggregation was induced by 50 μM ADP (adenosine diphosphate) optical platelet aggregation [16]. In the same study carprofen, meloxicam and non-selective NSAID aspirin administration did not significantly affect maximal platelet aggregation in the dogs, and overall there were no other significant findings regarding these NSAIDs and their effects on haemostatic measures including platelet number, Hct, PT, aPTT, plasma TXB_2, PGI_2 and 6-keto PGF_1.

4. DISCUSSION

The administration of NSAIDs and the associated development of adverse effects in animals are widely accepted. However, it was noted that there were variable findings in comparing the adverse effects associated with COX-2 selective NSAIDs and non-selective NSAIDs. COX-2 selective NSAIDs have been found associated with no adverse effects in some studies and minimal adverse effects in other studies. Severe adverse effects were reported for COX-2 selective NSAID administered at higher than recommended doses or for a long duration and some studies reported reduced adverse effects in COX-2 selective NSAIDs when compared to non-selective NSAIDs. Overall, gastrointestinal adverse effects were predominantly reported, followed by adverse findings relating to haemostasis and renal function.

Table 1. Summary of reported adverse effects of NSAIDs uses in animals

Study	A. NSAID Reported Adverse Effects in Horses	Animal No
Noble et al. 2012 [11]	**1. Meloxicam:**	*16 + 33 horses
	GI mucosal ulceration	*25 standard
D'Arcye et al. 2012 [6]	Decreased total serum protein	bred horses
	Decreased albumin concentrations	
	Gastrointestinal damage	
D'Arcy et al. 2012 [6]	**2. Phenylbutazone:**	*25 standard
	GI mucosal ulceration	bred horses
Noble et al. 2012 [11]	Hypoalbumaemia	*16 + 33 horses
	Neutropenia	*8 horses
McConnico et al. 2008 [7]	Right dorsal colitis	
	B. NSAID Reported Adverse Effects in Dogs	
Luna et al. 2007 [13]	**1. Meloxicam:**	*36 adult dogs
	Renal damage	
Blois et al. 2010 [16]	Increased bleeding, clotting time	*10 hound-
	Fibrinogen concentration decrease	crossbred dogs
Wooten et al. 2009 [9]	No decrease in platelet function	*8 dogs
	(No adverse effect)	
Roberts et al. 2009 [12]	**2. Deracoxib:**	*60 dogs
	Focal renal papillary necrosis	
Blois et al. 2010 [16]	(*Doses exceeding recommended dose)	*10 hound-
	Mild decrease in platelet function	crossbred dogs
Gordon et al. 2010 [17]	No improvement in recovery	*30 dogs
	Intense rehabilitation	
	(*After tibial plateau leveling osteotomy)	
Luna et al. 2007 [13]	**3. Carprofen:**	*36 adult dogs
	Increased bleeding	
Blois et al. 2010 [16]	Increased clotting time	*10 hound-
	Decreased serum protein	crossbred dogs
Raekallio et al. 2006 [14]	(*No effect on renal function)	*22 dogs
	(*No effect on hepatic function)	
Hazewinkel et al 2008 [15]	(*No decrease in platelet function)	*8 dogs
Blois et al. 2010 [16]	**4. Aspirin:**	*10 hound-
	No decrease in platelet function	crossbred dogs
Goodman et al. 2009 [8]	**5. Firocoxib:**	*6 mixed-bred
	Slowed GI wound healing	dogs
Moreau et al. 2005 [10]	Does not alter mucosal prostaglandin concentrations	*21 dogs
Hazewinkel et al 2008 [15]	Induced significant gastric and	*8 dogs
	Induced gastro-duodenal lesions in dogs that lacked pre-existing lesions	*8 dogs
Wooten et al. 2009 [9]	No adverse effects observed	
	Significantly reduced lameness	
Hazewinkel et al 2008 [15]	**6. Vedaprofen:**	*8 dogs
	No adverse effects observed	
Luna et al. 2007 [13]	**7. Etodolac:**	*36 adult dogs
	GI mucosal ulceration	
Luna et al. 2007 [13]	**8. Ketoprofen:**	*36 adult dogs
	GI mucosal ulceration	
	Increased bleeding, clotting time	
Luna et al. 2007 [13]	**9. Flunixin:**	*36 adult dogs
	Severe GI mucosal ulceration	
	Increased bleeding, clotting time	

Study	B. NSAID Reported Adverse Effects in Dogs	Animal No
Goodman et al. 2009 [8]	**10. Tepoxalin:** No effect on GI wound healing No suppression of mucosal LTB4 production	*6 mixed-bred dogs
Moreau et al. 2005 [10]	**11. Rofecoxib:** GI mucosal ulceration	*21 dogs
Moreau et al. 2005 [10]	**12. Licofelone:** No adverse effects on GI mucosa observed	*21 dogs

It should be noted that through the process of specifically selecting randomised controlled trials and excluding literature that failed to meet the inclusion criteria, the 12 included studies involved only horse and dog subjects. This is poor representation of the veterinary medicine current practice. As a result, conclusions made in this review may not be relevant to all species incorporated in veterinary practice. Additionally, it is likely that the published literature included in this review contains bias toward positive data for the intervention being studied. Furthermore, commercial funding of studies may be another source of bias in the literature. Also, there was much variability in duration of NSAID treatments in the included literature. As NSAIDs are commonly used in chronic disease cases such as osteoarthritis, NSAID therapy can be extended in clinical practice for a longer time frame than 6 months, which is the longest time period represented here; this is a limitation of this review and of the current peer-reviewed literature.

4.1 Effects on the Gastrointestinal System

Adverse effects related to the gastrointestinal system were the predominant adverse effect finding of the included literature. A 14 day-trial [6] was conducted on twenty-five standard bred horses, comparing the effect of oral administration of multiple dose rates of COX-2 selective NSAID, meloxicam, and non-selective NSAID, phenylbutazone, on gastric mucosal integrity. Outcomes were measured by sucrose permeability testing and findings were that a significant increase in serum sucrose concentration ($P = .001$) was identified in horses receiving phenylbutazone treatment compared to other treatment groups and baseline values, suggesting that phenylbutazone has a greater effect on mucosal integrity than meloxicam. A comparable study [11] investigated effects of phenylbutazone and meloxicam on mucosal integrity in horses for a longer duration of 42 days and some results were contradictory to the 14 day-trial. Administration of 3-5 times the recommended dose meloxicam was associated with gastrointestinal damage, although meloxicam administered at recommended dosage was well tolerated, thereby suggesting that the COX-2 selective NSAID meloxicam has dose-related adverse effects. Gastrointestinal adverse effects, including gastrointestinal mucosal ulceration and right dorsal colitis, were noted for phenylbutazone administration at the recommended dose rate in this study as well as in the 14 day-study. This finding of phenylbutazone adverse affects in two separate studies is of clinical importance as phenylbutazone is a commonly utilised NSAID in equine veterinary practice. Findings imply that the COX-2 selective NSAID meloxicam may be safer for use in practice compared to the non-selective NSAID phenylbutazone in order to minimise adverse effects.

In a study on adverse effects of long-term (90 days) oral administration of NSAIDs in dogs [13], COX-2 selective NSAIDs carprofen and meloxicam induced a lower frequency of gastrointestinal adverse effects compared to non-selective NSAIDs. In two separate studies [8,10] the effects of COX-2 specific NSAIDs were compared to newly developed COX and 5-lipoxygenase inhibitor, tepoxalin and licofelone in relation to gastric mucosa ulceration formation and healing in dogs. Both studies had similar findings in that dual COX and 5-lipoxygenase inhibitors had decreased gastrointestinal adverse effects compared to COX-2 specific NSAIDs. In the results of one study [10] it was also indicated that COX-2 selective NSAID adverse effects on GI mucosa and motility may not be related to PG suppression, but rather an unrelated mechanism as firocoxib did not alter mucosal prostaglandin concentrations compared with placebo, but slowed mucosal wound healing compared with both tepoxalin and placebo. This is an interesting finding that warrants further research.

4.2 Effects on the Cardiovascular System

In a study conducted on ten healthy hound-crossbred dogs [16], no significant effects on platelet function after aspirin, carprofen, and

meloxicam were found after 7 days of admission at the recommended dose rate. In the same study, deracoxib caused a mild decrease in platelet aggregation, although overall results indicated NSAID treatments did not affect platelet number, PT or APTT, and thromboxane B_2. These findings were not as expected. This was because aspirin is a COX-1 antagonist and is generally accepted to have antithrombotic effects as a result of irreversible acetylation of COX-1 in platelets, which in turn prevents thromboxane A_2 production [1,2,16]. Aspirin was therefore expected to have decreased platelet function, which was not seen in the results of this study. A mild decrease in platelet aggregation in association with deracoxib administration was also an unexpected result, which could be attributable to the small sample size, short duration or breed and age differences of the study. Further research is warranted to investigate effects of these NSAIDs on haemostasis in dogs.

4.3 Effects on the Renal System

Renal effects of NSAID were investigated in several studies by means of clinical pathology interventions [11-14,16]. Specifically, in one study involving 60 dogs administered COX-2 selective NSAID, deracoxib, post mortem histopathology revealed focal renal tubular degeneration and regeneration in some dogs receiving about 6 mg/kg/day [12]. Also focal renal papillary necrosis was seen in one dog treated with 8 mg/kg/day and in three dogs receiving 10 mg/kg/day. This study was the study of longest duration being 6 months, and doses of deracoxib were all above the maximum recommended dosage of 4 mg/kg /day. No other parameters of renal function were adversely affected in this study.

5. CONCLUSION

Collectively, absence of renal adverse effect reported in some studies may possibly be due to the fact that GI adverse effects often occur prior to signs of renal failure. As most studies included in this study have been conducted for no longer than a 6 month-period, thus a longer duration of study may have potentially resulted in detection of renal adverse effect indications. For better assessment of renal function, more specific diagnostics such as glomerular filtration should be used. Overall, COX-2 selective NSAIDs appear to provide a clinically useful improvement over non-selective NSAIDs as well as fewer adverse effects when given at recommended dose.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Monteiro-Steagall BP, Steagall PV, Lascelles BD. Systematic review of nonsteroidal anti-inflammatory drug-induced adverse effects in dogs. Journal of Veterinary Internal Medicine. 2013;27(5): 1011-1119.
2. Papich M. An update on nonsteroidal anti-inflammatory drugs (NSAIDs) in small animals. The Veterinary clinics of North America - Small Animal Practice. 2008; 38:1243-1266.
3. Khan SA, McLean MK. Toxicology of frequently encountered nonsteroidal anti-inflammatory drugs in dogs and cats. Veterinary Clinics of North America - Small Animal Practice. 2012;42:289-306.
4. Innes JF, Clayton J, Lascelles BD. Review of the safety and efficacy of long-term NSAID use in the treatment of canine osteoarthritis. The Veterinary Record. 2010; 166(8):226-230.
5. Moher D, Liberati A, Altman DG, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med. 2009;6(7): e1000097.
6. D'Arcy-Moskwa E, Noble GK, Weston LA et al. Effects of meloxicam and phenylbutazone on equine gastric mucosal permeability. Journal of Veterinary Internal Medicine. 2012;26(6):1494-1499.
7. McConnico RS, Morgan TW, Williams CC et al. Pathophysiologic effects of phenylbutazone on the right dorsal colon in horses. American Journal of Veterinary Research. 2008;69(11):1496-1505.
8. Goodman L, Torres B, Punke J et al. Effects of firocoxib and tepoxalin on healing in a canine gastric mucosal injury model. Journal of Veterinary Internal Medicine. 2009;23(1):56-62.
9. Wooten JG, Blikslager AT, Marks JM et al. Effect of nonsteroidal anti-inflammatory drugs with varied cyclooxygenase-2 selectivity on cyclooxygenase protein and prostanoid concentrations in pyloric and duodenal mucosa of dogs. American

Journal of Veterinary Research. 2009; 70(10):1243-1249.
10. Moreau M, Daminet S, Martel-Pelletier J et al. Superiority of the gastroduodenal safety profile of licofelone over rofecoxib, a COX-2 selective inhibitor, in dogs. Journal of Veterinary Pharmacology and Therapeutics. 2005;28(1):81-86.
11. Noble G, Edwards S, Lievaart J et al. Pharmacokinetics and safety of single and multiple oral doses of meloxicam in adult horses. Journal of Veterinary Internal Medicine. 2012;26(5):1192-1201.
12. Roberts ES, Van Lare KA, Marable BR et al. Safety and tolerability of 3-week and 6-month dosing of Deramaxx (deracoxib) chewable tablets in dogs. Journal of Veterinary Pharmacology and Therapeutics. 2009;32(4):329-337.
13. Luna SPL, Basílio AC, Steagall PVM, et al. Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. American Journal of Veterinary Research. 2007;68(3):258-264.
14. Raekallio MR, Hielm-Bjorkman AK, Kejonen J et al. Evaluation of adverse effects of long-term orally administered carprofen in dogs. Journal of the American Veterinary Medical Association. 2006; 228(6):876-880.
15. Hazewinkel HA, van den Brom WE, Theyse LF, et al. Comparison of the effects of firocoxib, carprofen and vedaprofen in a sodium urate crystal induced synovitis model of arthritis in dogs. Research in Veterinary Science. 2008;84(1):74-79.
16. Blois SL, Allen DG, Wood RD et al. Effects of aspirin, carprofen, deracoxib, and meloxicam on platelet function and systemic prostaglandin concentrations in healthy dogs. American Journal of Veterinary Research. 2010;71(3):349-358.
17. Gordon-Evans WJ, Dunning D, Johnson AL. Randomised controlled clinical trial for the use of deracoxib during intense rehabilitation exercises after tibial plateau levelling osteotomy. Veterinary and Comparative Orthopaedics and Traumatology. 2010;23(5):332-335.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history/27839