Scientific Works. Series C. Veterinary Medicine. Vol. LXV (1), 2019
ISSN 2065-1295; ISSN 2343-9394 (CD-ROM); ISSN 2067-3663 (Online); ISSN-L 2065-1295

STUDY ON CHANGES IN HAEMATOLOGICAL PARAMETERS FOLLOWING ADMINISTRATION OF NSAIDs IN DOGS

Ionuț Răzvan DOBRE, Diana Mihaela ALEXANDRU, Maria CRIVINEANU

University of Agronomic Sciences and Veterinary Medicine of Bucharest, 59 Marasti Blvd, District 1, Bucharest, Romania

Corresponding author email: drrazvandobre@gmail.com

Abstract

NSAIDs have the ability to suppress the inflammatory process. They have antithrombotic action at low doses, analgesic and antipyretic action at medium doses and anti-inflammatory effects at elevated doses. Whereas the beneficial effects of NSAIDs are often overshadowed by the adverse effects, the aim of the study is to track side effects on hematology parameters after administration of anti-inflammatory NSAIDs in dogs. The study was performed on 8 dogs, male and female, of different races and ages, to whom were administered Flunixin, Metacam and Carprofen. The side effects on haematological parameters were observed and analyzed, when given medication as prescribed. In the case of Flunixine, increased white blood cell counts and decreased number of red blood cells, hematocrit have been observed. Metacam and Carprofen caused a lower decrease in hematocrit and red blood cell counts, as well as increased leucocyte counts. In all cases, a decrease in platelet count and a prolongation of prothrombin time were observed. This study conducted to the conclusion that the substances used didn't cause significant haematological changes, at the same time having a constant antithrombotic action and favouring coagulopathies.

Key words*: NSAIDs, dog, osteoarthritis, haematological parameters.*

INTRODUCTION

Anti-inflammatory, analgesic and antipyretic drugs comprise a heterogeneous group of compounds with different chemical structure but with similar pharmacological effects and side effects (KuKanich et al., 2012).

All drugs in this group associate, in varying proportions, analgesic, anti-inflammatory and antipyretic actions. These can be used either as symptomatic drugs in fever and pain conditions, or for anti-inflammatory action in rheumatic conditions (Jones et al., 2002; Watson et al., 1996).

The actions of these substances are attributed to the metabolic effect of diminishing prostaglandin synthesis as a consequence of cyclooxygenase inhibition. Cyclooxygenase is the enzyme which catalyses the oxidative cyclization of arachidonic acid with the formation of cyclic endoperoxides, which are precursors of prostaglandins, thromboxanes and prostacyclin (Lascelles et al., 1998).

Recent data has indicated that cyclooxygenase, which is the central enzyme of prostanoid biosynthesis, exists in two forms: COX_1 and COX_2. COX_1 is present in normal tissues and involved in the formation of prostaglandins that protect the stomach and intestinal mucosa against the harmful effects of gastric acid, promotes blood clotting by activating platelets and maintains good kidney function (Ngo & Addison, 2018; Wallace et al., 1990).

COX_2 plays a role in the secretion of prostaglandins involved in inflammation, pain and fever, is present in all inflamed tissues and its formation is induced by cytokines (Bree et al., 1994).

Classical non-steroidal anti-inflammatory drugs inhibit both types of cyclooxygenases (COX_2 inhibition justifies pharmacodynamic effects while inhibition of COX_1 induces most adverse effects). They are commonly used to treat orthopedic problems in dogs but at the same time they are account for about 8% of all officially recorded intoxications (Dharmaceelan et al., 2018).

Recently, non-steroidal anti-inflammatory drugs have been synthesized that selectively inhibit COX_2, thus achieving the desired pharmacodynamic effects with minimal adverse reactions (Luna et al., 2007; McCann et al., 2004).

The anti-inflammatory effect of these substances is proportional to the cyclooxygenase inhibitory capacity (Borer et al., 2003).

The purpose of the study was to monitor the clinical effects and possible adverse reactions following the use in the therapy of osteoarticular disorders of non-steroidal anti-inflammatory drugs. Studies conducted so far in dogs have shown that side effects are minimal in this species, being mainly due to digestive disorders and very rare nephrotoxicity.

MATERIALS AND METHODS

The experiment was performed in a veterinary clinic and the haematological examination in the laboratory of the Faculty of Veterinary Medicine in Bucharest. The study was conducted on 8 cases of dogs, males and females of different ages, who after clinical and paraclinical examinations were diagnosed with different orthopedic problems.

Non-steroidal anti-inflammatory drugs used to study haematological changes following administration in dogs were:

- Flunixine (Flunixin meglumine), 100 ml vials containing 50 mg flunixin meglumine / ml.
- Metacam (Meloxicam), 100 ml suspension for oral administration containing 5 mg meloxicam / ml.
- Rimadyl (Carprofen), vials with 20 ml of oily suspension for injection containing 50 mg carprofen / ml.

Flunixin meglumine is part of the carboxyl group and the administration period recommended by the manufacturer for dogs is 5 days (Erdogan et al., 2003).

Metacam (meloxicam) belongs to the group of enolic acids and Carprofen belongs to the group of carboxylic acids. These two preparations may be administered for a longer period of time (Doig et al., 2000).

Secondary effects (haematological changes) were observed under non-steroidal anti-inflammatory drug therapy using the therapeutic dose.

The three non-steroidal anti-inflammatory drugs used were administered as follows:

- flunixin meglumine was administered subcutaneously at the dose of 1.1 mg / kg for 7 days;
- meloxicam was orally administered at a dose of 0.1 mg / kg for 30 days;
- carprofen was administered subcutaneously at the dose of 4 mg / kg for 30 days.

In all cases, anti-inflammatory substances have been administered as a single therapy without resorting to association with other medicinal products.

Prior to drug administration, 7 days after flunixin meglumine administration, 15 and 30 days after Carprofen and Meloxicam administration blood samples were taken from all subjects in order to determine hemoglobin, hematocrit, number of red blood cells, leukocytes, platelets, reticulocytes, leukocyte formula and prothrombin time (Quick).

RESULTS AND DISCUSSIONS

Following the haematological examinations performed, the following results were obtained, as shown in Tables 1, 2 and 3:

Table 1. The average values of hematology parameters in dogs following administration of Flunixin meglumine

Parameters	Reference values	Before treatment	7 days after treatment
Hemoglobin (g/dl)	12-18	14.60	13.80
Hematocrit (%)	37-55	46.70	44.60
RBC count	5.5-8.5 x 1,000,000	4,948,000	4,760,000
Platelets count	1.75-5 x 100,000	255,300	310,400
Reticulocyte (%)	0-1.5	12.5	24.5
Leukocytes count	6-17 x 1,000	11,240	12,100
Neutrophils (%)	3.6-11.5 x 1000	54.8	61.2
Eosinophils (%)	0.01-1.25 x 1000	3.4	2.2
Basophils (%)	0.0-0.3 x 1000	2.7	2
Lymphocytes (%)	1.0-4.8 x 1000	29.1	27.3
Monocytes (%)	0.15-1.35 x 1000	9.9	7.2
Quick time (seconds)	11-17	13.6	14.8

Table 2. The average values of hematology parameters in dogs following administration of Meloxicam

Parameters	Reference values	Before treatment	15 days after treatment	30 days after treatment
Hemoglobin (g/dl)	12-18	14.54	13.35	13.24
Hematocrit (%)	37-55	49.6	43.8	45.6
RBC count	5.5-8.5 x 1,000,000	4,772,000	4,672,000	4,770,000
Platelets count	1.75-5 x 100,000	164,000	192,200	247,000
Reticulocyte (%)	0-1.5	15.8	28.6	31.3
Leukocytes count	6-17 x 1,000	10,800	11,630	12,350
Neutrophils (%)	3.6-11.5 x 1000	61.6	59.2	52.6
Eosinophils (%)	0.01-1.25 x 1000	6.3	6.1	6.9
Basophils (%)	0.0-0.3 x 1000	0	0	0
Lymphocytes (%)	1.0-4.8 x 1000	27.4	31	34
Monocytes (%)	0.15-1.35 x 1000	4.6	3.6	6.4
Quick time (seconds)	11-17	11.4	13.6	14.4

Table 3. The average values of hematology parameters in dogs following administration of Carprofen

Parameters	Reference values	Before treatment	15 days after treatment	30 days after treatment
Hemoglobin (g/dl)	12-18	15.35	15.22	13.85
Hematocrit (%)	37-55	47.8	47	45.4
RBC count	5.5-8.5 x 1,000,000	4,884,000	4,866,000	4,714,000
Platelets count	1.75-5 x 100,000	174,000	190,000	305,000
Reticulocyte (%)	0-1.5	11.25	18.8	29
Leukocytes count	6-17 x 1,000	7,940	8,360	10,460
Neutrophils (%)	3.6-11.5 x 1000	51.6	53.4	63.2
Eosinophils (%)	0.01-1.25 x 1000	5.2	6.1	5.8
Basophils (%)	0.0-0.3 x 1000	0	0	0
Lymphocytes (%)	1.0-4.8 x 1000	37.3	36	27.7
Monocytes (%)	0.15-1.35 x 1000	5.8	4.4	3.2
Quick time (seconds)	11-17	11.11	13.2	15.2

When flunixin meglumine was administered to dogs with various osteoarticular disorders, were observed a decrease in hematocrit and number of red blood cells, increased white blood cell counts, increased neutrophil count and decreesed lymphocytes, and a significant increase in platelet count and prothrombin time (Quick).

Following administration of Meloxicam resulted in a more pronounced decrease in hematocrit compared to the Flunixin administration, increased platelet count and leucocyte counts, neutrophil decrease and lymphocyte growth and a slight increase in Quick Time.

Following the administration of Carprofen to dogs with osteoarticular disorders, were observed a slight decrease in hematocrit and number of red blood cells, significant increase in platelet counts, increased white blood cell count and neutrophil count, decreased lymphocyte count and prolonged Quick Coagulation Time.

Of all the investigated animals with osteoarthritis at various stages, hematological parameters following administration of non-steroidal anti-inflammatory drugs, determined at different time intervals from the start of treatment, experienced greater or smaller variations as can be seen from the following graphs (Figures 1, 2, 3, 4, 5 and 6).

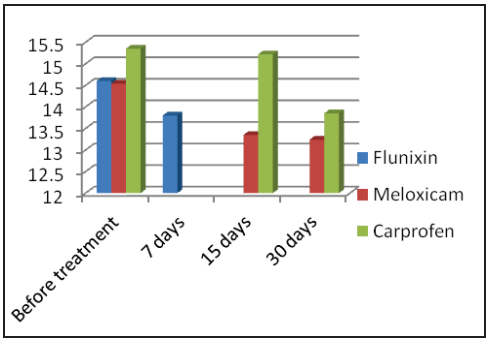

Figure 1. Average hemoglobin values during treatment with the three products

It is noted that all average values of hemoglobin remain within the reference limits,

with a more pronounced decrease in Meloxicam and Carprofen products.
All average hematocrit values are within the reference limits, a more significant variation being observed for meloxicam.
The average number of red blood cells is slightly below the reference range, with no significant variation in the time of therapy with these pharmaceuticals.
The average number of red blood cells is slightly below the reference range, with no significant variation in the time of therapy with these pharmaceuticals.
Average platelets values remain throughout the study within the reference limits, the slight increase had no clinical significance.
Likewise, leukocytes are placed within the reference range at all times of the assay, the growth trend being not significant.

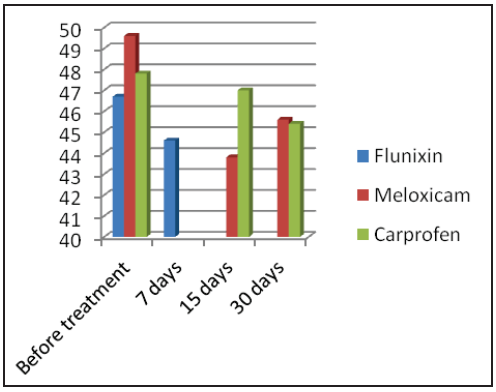

Figure 2. Average values of hematocrit during the studied period

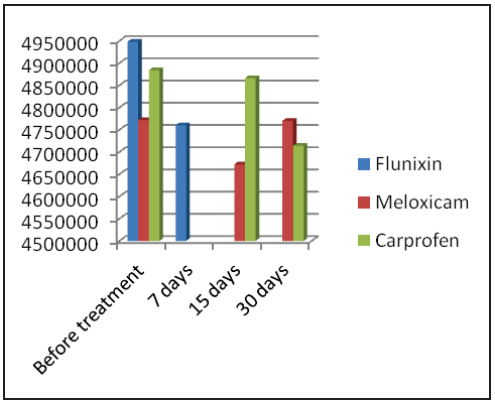

Figure 3. Average values of red blood cells during the study

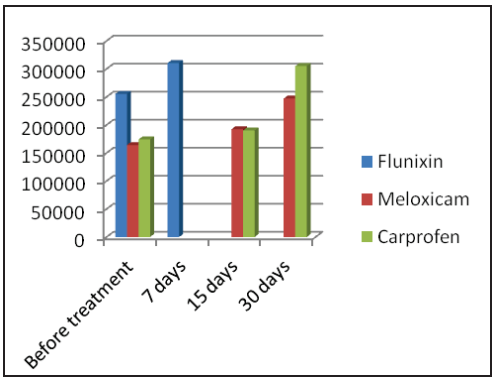

Figure 4. Average platelet values during the study period

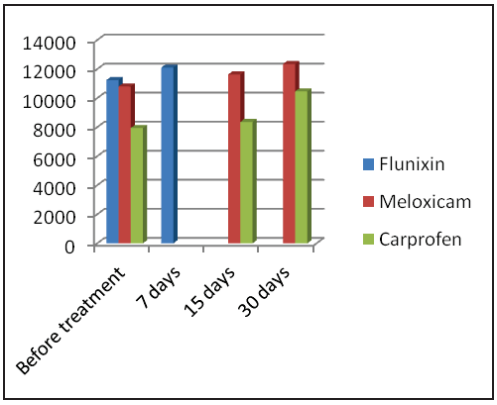

Figure 5. The average values of leukocytes during the administration of the anti-inflammatory drugs studied

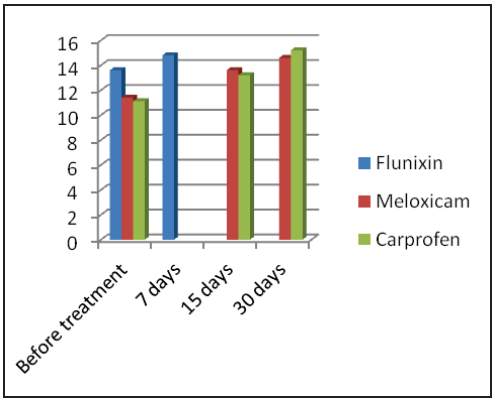

Figure 6. Average values of prothrombin time (Quick) during the study period

In the case of prothrombin time, it is placed in the reference range until the last determination but, in all cases, a trend of prolongation (coagulopathy tendency) is observed.

CONCLUSIONS

The experiment conducted on a number of 8 dogs with osteoarticular disease followed the hematological side effects of 3 NSAIDs with different chemical structures and similar action mechanisms.

From the determinations made with the three substances, there is a constant increase in the prothrombin time (coagulopathy) and insignificant alterations of the other parameters. Comparative study of changes in haematological parameters in the use of the 3 substances showed that the least changes occurred with the use of flunixin meglumine followed by carprofen and meloxicam.

Studies have shown that preparations of the non-steroidal anti-inflammatory drug used in dogs do not cause obvious haematological changes.

REFERENCES

Borer, L.R., Peel, J.E., Seewald, W., Schawalder, P., & Spreng, D.E. (2003). Effect of carprofen, etodolac, meloxicam, or butorphanol in dogs with induced acute synovitis. American journal of veterinary research, 64(11). 1429-1437.

Bree, H. Van, Justus, C., Quirke, J.F. (1994). Preliminary observation on the effects of meloxicam in a new model for acute intraarticular inflammation in dogs. Veterinary Research Communication, 18(3). 217-224.

Dharmaceelan, S., Manikandan, R., Jayakumar, K., Senthilkumar, S., & Selvaraj, P. (2018). Haemato-biochemical alterations and stress response to pre-emptive administration of meloxicam, ketoprofen, tolfenamic acid and flunixin in dogs. The Pharma Innovation Journal,7(11). 218-221.

Doig, P.A., Purbrik, K.A., Hare, H.F., Mc Keown, D.B. (2000). Clinical efficacy and tolerance of meloxicam in dogs with chronic osteoarthritis. Canadian Veterinary Journal, 4(4). 296-300.

Erdogan, H.M., Gunes, V., Gorkce, H.I., Uzun, M., Citil, M., Yuksek, N. (2003). Effects of prolonged intravenous of flunixin meglumine in healthy dogs. Acta Veterinaria Brno, 72(1). 71-78.

Jones, C.J., Streppa, H.K., Harmon, B.G., Budsberg, S.C. (2002). In vivo effects of meloxicam and aspirin on blood gastric mucosal and synovial fliud prostanoid synthesis in dogs. American Journal of Veterinary Research, 63(11). 1527-1531.

KuKanich, B., Bidgood, T., & Knesl, O. (2012). Clinical pharmacology of nonsteroidal anti-inflammatory drugs in dogs. Veterinary anaesthesia and analgesia, 39(1). 69-90.

Lascelles, B.D.X., Cripps, P.J., Jones, A., Waterman-Pearson, A.F. (1998). Efficacy of kinetics carprofen administred preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterotomy, Veterinary Surgery, 27(6). 568-582.

Luna, S.P., Basílio, A.C., Steagall, P.V., Machado, L.P., Moutinho, F.Q., Takahira, R.K., & Brandão, C.V. (2007). Evaluation of adverse effects of long-term oral administration of carprofen, etodolac, flunixin meglumine, ketoprofen, and meloxicam in dogs. American journal of veterinary research, 68(3). 258-264.

McCann, M.E., Donald, R., Zhang, D., Brideau, C., Black, W.C., Hanson, P.D., & Hickey, G.J. (2004). In vitro effects and in vivo efficacy of a novel cyclooxygenase-2 inhibitor in dogs with experimentally induced synovitis. American journal of veterinary research, 65(4). 503-512.

Ngo, S.N., & Addison, C.J. (2018). Are COX-2 Selective NSAIDs Associated with Less GI, Renal, and Cardiovascular Side Effects: Evidence from Animals Treated with NSAIDs. Annual Research & Review in Biology, 1-8.

Wallace, M.S., Zawie, D.A., Garvey M.S. (1990). Gastric ulceration in the dog secondary to use of nonsteroidal anti-inflamatory drugs. J. Am. Anim. Hosp. Assoc., 26. 467-472.

Watson, A.D.J., Nicholson, A., Church, D.B., & Pearson, M.R.B. (1996). Use of anti‐inflammatory and analgesic drugs in dogs and cats. Australian veterinary journal, 74(3). 203-210.