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MELOXICAM-INDUCED GASTROPATHY IN DOGS: CLINICAL, HEMATO-BIOCHEMICAL, ENDOSCOPIC FEATURES AND TRIALS FOR PREVENTION

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Abstract: This study was conducted to evaluate and to compare the clinical, hemato-biochemical and endoscopic aspects of gastropathy in dogs treated with meloxicam alone or incombination with esomeprazole and misoprostol. Twenty baladi healthy dogs were included in the experimental study. Dogs were divided into four groups each group consisting of five animals; Group I (control group), the group that does not receive any medication. Meloxicam treated groups divided into: Group II which received meloxicam at a dose of 0.2 mg/kg BWT per OS /24 hr. Group III animals received the same previous dose of meloxicam and esomeprazole at a dose of 1mg/kg BWT per OS /24 hr. Group IV animals received the same dose of meloxicam and misoprostol 3µg /kg BWT per OS tid. Upon drug administration, dogs were kept under observation for 14 consecutive days. Clinical and hemato-biochemical analysis were evaluated across time (T0, T3, T7, T10 and T14). The image analysis of the gastroscopic examination was evaluated across time (T0, T7 and T14), endoscopic examinations were applied to all animals in four groups at three time points (T0, T7, and T14), endoscopic lesions were scored by use of a 5-point scale. Clinically, the most common clinical sings in dogs with Meloxicam induced- gastropathy were inappetence to anorexia, hematemesis, melena, abdominal pain and weakness, the specific endoscopic lesions of gastropathy were gastric erosion, hemorrhage and ulcers. Serum gastrin concentration is a biochemically sensitive indicator of gastropathy. The overall results concluded that meloxicam-induced gastropathy was more severe in group II compared to groups III and group IV. The proton pump inhibitor (esomeprazole) was more effective and better tolerated than misoprostol.

Key words: endoscopy; esomeprazole; gastropathy; meloxicam; misoprostol

Introduction

There have been numerous reports of nonsteroidal anti-inflammatory drug (NSAID)-related gastric abnormalities in humans, known as NSAID-gastropathy. Gastritis and gastropathy are conditions that affect the gastric mucosa. In gastritis, the stomach lining is inflamed and in gastropathy, the stomach lining is damaged, but with little or no inflammation (1). NSAID-gastropathy is characterized by subepithelial hemorrhages, erosions, and ulcers (2). NSAID are commonly used in human and animal treatment. Its adverse effects widely involve the gastrointestinal tract, the most important adverse effect is development of ulcers especially in the stomach, and the presence of such lesions is often unpredictable because the clinical signs may be missed until the complication develops (3).

Meloxicam is a new and the most commonly prescribed NSAID for canine in Egypt. It is a potent inhibitor of prostaglandin synthesis that has anti-inflammatory, analgesic, and antipyretic properties (4, 5). Meloxicam has slightly greater activity against COX-2 than against COX-1(6). Because of preferential COX-2 inhibition, meloxicam was superior regarding postoperative pain control in dogs (7). Along with the desired effects of meloxicam, the systemic inhibition of

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PGE2 production inhibits the normal mechanisms of the gastric mucosa protection. In the absence of the protective mechanisms, the stomach acidic environment damages gastric mucosa leading to gastropathy (8). Many reports were recorded about gastric erosion, ulceration or even perforation associated with meloxicam administration in dogs (9,10,11).

The diagnosis of canine gastropathy is based on the history, clinical, hemato-biochemical, radiography, and ultrasonography (12). There is no correlation between NSAID gastropathy and upper abdominal symptoms frequently. So, medical endoscopy has emerged as a key technology for minimally-invasive examinations for gastropathy. Using endoscopy, gastroduodenal lesions are identified including subepithelial hemorrhages and erosions not only ulcers (10,13) Gastroprotectants are drugs used in veterinary medicine secondary to administration of NSAIDs including meloxicam. Because of the various benefits and good efficacy of NSAIDs, many drugs have been developed to decrease gastric acid secretion and/or promote mucosal protective defenses to prevent and treat ulcerations. The most commonly used drugs are the prostaglandin analogues such as misoprostol, which is an antiulcer drug, and proton pump inhibitors, as esomeprazole whose efficacy in preventing NSAID-associated ulcers has been recently demonstrated (14). Therefore, the aims of this study are to evaluate and compare the clinical, hemat-biochemical and endoscopic aspects of gastropathy in dogs treated by meloxicam alone or coadministered with esomeprazole and misoprostol.

Material and methods

Ethical statement

All the experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC), Zagazig University (Approval No. ZU-IACUC/ 2/F/18/2022).

Experimental design, animal management and feeding regime.

The experiment was carried out at the experimental animal unit of the Faculty of Veterinary Medicine, Zagazig University, Egypt. This study was applied on 20 male baladi dogs their body weight (20-25 kg BWT) and age ranged from 8-12 months. On admission physical examination was conducted for all animals. The animals were housed for 15 days to acclimatize and were monitored during this period. All dogs were vaccinated and treated with an appropriate anthelmintic (praziquantel [Drontal], 5 mg/kg PO). All groups were reared in uniform nutritional and management conditions. They were supplied with adlibitum diet (meat and chicken extract) and had free access to water.

Drug used

- Meloxicam (tablets, 7.5 mg).

Commercial name; Medexaflam 7.5 mg (GPI pharma - EGYPT). Dose: (0.2 mg/kg BWT) per os /24 hr. (9).

- Esomeprazole (capsule, 40 mg), Proton pump inhibitor

Commercial name: Esmorap 40 mg (AUG pharma -EGYPT). Dose: (1mg/kg BWT)/24hr per os (15).

- Misoprostol (tablets, 200 µg).

Commercial name: Misotac tablet 200 µg (Sigma pharma -EGYPT). Dose: (3µg /kg BWT) 3 times daily orally (16).

Animals grouping

After passing the acclimatization period, the dogs divided randomly into four groups each consisting of five animals.

- Group I (control group).
- Group II (Meloxicam)
- Group III (Meloxicam+ Esomeprazole)
- Group IV (Meloxicam+ Misoprostol)

Clinical examination

Clinical examination and vital signs monitoring were thoughtfully performed for all animals in the four groups at different time periods (T0, T3, T7, T0 and T14) with closed daily observation to any clinical abnormalities.

Hemato-biochemical screening

Two blood samples were collected from each animal in the four groups at five different time

points (T0, T3, T7, T0 and T 14) via cephalic vein puncture. For hematological studies, 2 mL of blood was taken into (k2 EDTA) tubes, red blood cells (RBCs) count, hemoglobin (Hb) concentration, packed cell volume (PCV), platelets count, total leucocytic counts and neutrophil percent were measured using full version automatic cell counter (Sysmex KX-21N, Japan) according to the method of (17). The other blood sample of 5 ml was taken in plain tubes without anticoagulant for serum separation for making biochemical analysis. Serum total protein and albumin were determined spectrophotometrically by standard procedures using (Diagnostic Zrt. Commercial kits) provided by Biomerieux, Egypt. Serum gastrin was performed via the GASTRIN (125 I) Radioimmunoassay Kit (MP Biomedicals, USA). According to (18). Serum IL1 Beta was estimated by using a quantitative sandwich enzyme immunoassay technique according to the manufacture of CUSABIO.

Endoscopic examination Preparation of animals

A more updated protocol was applied; the food was withheld for 24 hrs and water was withheld 6 hrs before anesthesia (19). Atropine sulfate (MISR CO.EGYPT) at a dose 0.05mg/kg SC and 2% xylazine HCL (ADWIA, 10th of Ramadan City, Egypt) at a dose of 0.5 mg/kg BW I/M.

The endoscopy procedure

All dogs were examined by endoscopy at 3 time points (T0, T7 and T14). At T0 to assess the presence of any visible lesions before the experiment (19,20).The dogs were anaesthetized for endoscopic examination, general anesthesia was induced with I/V injection of thiopental sodium 2.5% (Thiopental Sodium, EIPICO, 10th of Ramadan city) at a dose of 25 mg/kg BW. The upper gastrointestinal tract was examined using a Porta scope endoscope (PVSM3M, Florida), the endoscopic examination being the same on all occasions starting by the esophagus, followed by the stomach body, the antrum/body junction and the antrum and then duodenum. The images of the mucosa at these sites were videotaped. Presence of any erosions, hemorrhage and/ or ulcerations were recorded (20). A subjective endoscopic severity scoring system has been established in which a stomach with no visible lesions is scored as 0; a stomach with a few submucosal petechia but no visible defects in the mucosa is scored as 1, a stomach with few erosions is scored as 2, stomach with extensive areas of erosions is scored as 3, and a stomach with an ulcer of any size is scored as 4 modified from (21).

Statistical analysis

Data of hemato-biochemical parameters were statistically analyzed with one-way analysis of variance (ANOVA) using a statistical software program (SPSS for Windows, version 16.0, SPSS Inc., Chicago, IL). Duncan's post-hoc test was used to determine the level of significance between the four groups. Results were expressed as means ± SE and were considered statistically significant when $p<0.05$.

Results

Clinical Findings:

Clinical findings were recorded daily during the experiment. The reported findings are presented in Table 1. In group II, the recorded findings include mild inappetence and anorexia, hematemesis, occult blood, melena, signs of colic and abdominal pain manifested as arching of the back and sitting on the hindquarters, congested mucous membrane, dullness and depression, weakness and emaciation, shock, distended abdomen and death in 1 dog. In group III, only inappetence is observed in 1 dog while in group IV, transient diarrhea, inappetence and occult blood were recorded. Regarding vital signs, no remarkable changes were recorded in body temperature, pulse, and respiratory rates and their values were within the reference range in the four groups at different time points except 1 dog, the dog was febrile, tachycardic and tachypneic and hypothermic. It is worthy to mentioned that 1 dog with a gastric ulcer showed mild clinical signs

Hemato-biochemical findings:

The results of hematological and biochemical parameters are shown in Table. 2, 3 there were a significant decrease ($P<0.01$) in Hb, RBCs and PCV were recorded in group II at T10 when compared with other groups, whilea significant decrease

Table 1: Clinical findings were recorded daily during the experiment in the control and the three experimental groups

Items		Control group Group I % (N/5)	Experimental groups %(N/T)		
			Group II (n=5)	Group III (n=5)	Group IV(n=5)
Diarrhea	%(N/T)	0% (0/5)	0% (0/5)	0% (0/5)	60 % (3/5)
	Onset	----------	----------	----------	4 th to 7 th day
Inappetence to anorexia	%(N/T)	0% (0/5)	60% (3/5)	20% (1/5)	40 % (2/5)
	Onset	----------	7 th to 14th day	14t th day	12 th day
Hematemesis	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	8 th day	----------	---------
Occult blood* or melena	%(N/T)	0% (0/5)	60% (3/5)	0% (0/5)	20% (1/5)
	Onset	----------	8 th day	----------	12 th day
Congested mucous membrane	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	9th day	--------	---------
Dehydration	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	9 th day	----------	---------
Dullness and depression	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	9 th day	---------	-------
Weakness &emaciation	%(N/T)	0% (0/5)	40% (2/5)	0% (0/5)	0% (0/5)
	Onset	----------	9 th day	----------	---------
Shock	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	10th day	----------	----------
Colic signs	%(N/T)	0% (0/5)	40% (2/5)	0% (0/5)	20% (1/5)
	Onset	----------	9 th and 11th to 14 day	---------	11 th day
Distended abdomen	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	10 th day	--------	---------
Death	%(N/T)	0% (0/5)	20% (1/5)	0% (0/5)	0% (0/5)
	Onset	----------	11 th day	---------	---------

($p<0.05$, $p<0.01$ and $p<0.01$) respectively at T14 was recorded in the three experimental groups in comparison with control group, with the lowest value in the meloxicam treated group. Platelets was significantly decreased ($P<0.05$) at T7 in group II in comparing with groups I, III and IV. While, at T10 and T14 a highly significant decrease ($P<0.01$) was recorded in the three experimental groups in comparison with control group with the lowest value in group II. Regarding WBCs, significantly increased ($P<0.01$) at T10 and T14 in the meloxicam treated groups with the highest value in group II, significant increase in WBCs ($P<0.05$) at T10 was recorded in group II in comparing with group I, III, IV. While a highly significant increase ($P<0.01$) at T 14 was recorded in the three experimental groups in comparison with control group with the highest value in group II.

Serum gastrin recorded a significant increase ($P<0.05$ and $P<0.01$) at T3 and T7 in group II in comparison with the remaining groups. A highly significant increase ($P<0.01$) in serum gastrin was recorded at T10 and T14 n the three experimental groups in comparison with control group with the highest value in the meloxicam treated group. Serum IL-1β was significantly increased ($P<0.05$ and $P<0.01$) respectively at T10 and T14 in the three experimental groups in comparison with control group with the highest value in group II. TNF-α recorded significant increase ($P<0.05$) at T3 in group II in comparison with group I, III and IV, while at T7, T10 and T 14 a highly significant increase in TNF-α ($P<0.01$) in the three experimental groups in comparison with control group. A significant decrease ($P<0.05$) in total protein was recorded at T4 in comparison

Table 2: Means and SE of hematological parameters in control and experimental group at five time points

Items		Group 1 (control)	Experimental groups			P-value
			group 2 (Meloxicam)	group 3 (Melox.+ Esmop.)	group 4 (Melox.+ Misop.)	
Hemoglobin (g/dl)	Day 0	15.17 ± 1.041	15.37 ± 0.651	15.04 ± 1.178	15.53 ± 1.301	**0.943**
	Day 3	15.23 ± 0.681	15.52 ± 0.912	15.02 ± 1.433	15.34 ± 1.634	**0.967**
	Day 7	15.37 ± 0.862	13.87 ± 1.629	14.99 ± 1.770	15.27 ± 1.966	**0.663**
	Day 10	15.20 ± 0.755^{a}	11.24 ± 0.966^{b}	14.81 ± 1.409^{a}	14.52 ± 0.951^{a}	**0.006**
	Day 14	15.00 ± 1.058^{a}	11.03 ± 1.750^{b}	12.53 ± 0.586^{b}	12.51 ± 1.115^{b}	**0.023**
RBCs (cell/ microliter)	Day 0	6.167 ± 0.404	6.100 ± 0.265	6.000 ± 0.500	5.967 ± 0.306	**0.910**
	Day 3	6.067 ± 0.551	5.967 ± 0.764	5.967 ± 0.351	5.767 ± 0.551	**0.930**
	Day 7	5.900 ± 0.819	5.367 ± 0.850	5.933 ± 0.551	5.667 ± 0.651	**0.765**
	Day 10	6.100 ± 0.361^{a}	4.040 ± 0.505^{b}	5.867 ± 0.351^{a}	5.400 ± 0.400^{a}	**0.001**
	Day 14	6.233 ± 0.709^{a}	4.167 ± 0.252^{b}	4.667 ± 0.231^{b}	4.467 ± 0.709^{b}	**0.006**
PCV (%)	Day 0	46.33 ± 4.163	45.33 ± 4.163	48.00 ± 3.606	47.33 ± 4.163	**0.858**
	Day 3	47.67 ± 3.512	44.67 ± 3.786	47.67 ± 7.095	47.00 ± 4.583	**0.860**
	Day 7	46.00 ± 6.557	39.67 ± 5.033	46.00 ± 3.606	46.67 ± 4.726	**0.353**
	Day 10	47.00 ± 4.359^{a}	29.67 ± 4.509^{b}	44.00 ± 2.646^{a}	46.00 ± 3.606^{a}	**0.002**
	Day 14	47.00 ± 3.606^{a}	29.33 ± 1.528^{c}	38.67 ± 3.055^{b}	36.67 ± 1.528^{b}	**0.000**
WBCs (cell/ microliter)	Day 0	7.667 ± 0.473	7.833 ± 1.097	7.610 ± 0.609	7.870 ± 0.814	0.970
	Day 3	7.867 ± 0.907	7.767 ± 1.290	7.700 ± 0.572	7.967 ± 0.764	0.985
	Day 7	7.833 ± 1.102	8.433 ± 0.808	8.000 ± 1.249	8.067 ± 0.586	0.891
	Day 10	7.933 ± 0.850^{b}	11.18 ± 1.301^{a}	9.167 ± 0.764^{b}	9.313 ± 0.697^{b}	0.018
	Day 14	7.767 ± 1.002^{c}	13.90 ± 0.715^{a}	10.87 ± 0.808^{b}	11.27 ± 1.102^{b}	0.000
Neutrophils (%)	Day 0	60.67 ± 7.638	61.33 ± 2.517	60.30 ± 7.292	62.33 ± 9.074	0.985
	Day 3	61.33 ± 8.083	63.00 ± 5.000	64.33 ± 10.02	64.04 ± 8.203	0.966
	Day 7	61.67 ± 11.59	62.50 ± 7.365	66.67 ± 8.737	65.10 ± 8.350	0.899
	Day 10	61.00 ± 10.15	77.67 ± 5.859	70.33 ± 5.686	66.94 ± 7.111	0.121
	Day 14	61.67 ± 8.327^{b}	83.33 ± 5.033^{a}	78.00 ± 6.000^{a}	80.33 ± 5.132^{a}	0.012

with group I, III, IV. and albumin and at T7, T10 a significant decrease (P<0.05) in albumin and at T7, T10 was recorded in group II when compared with group I, III and IV while at T 14 a significant decrease (P<0.01), was recorded in albumin in the three experimental groups in comparison with control group with the lowest value in group II.

Endoscopic findings:

Table 4. and Figure 1 (a-e) explain the endoscopic features in this study. In group I, a normal endoscopic image showed gastric rugal folds of the stomach, gastric mucosa thrown into folds, folds larger on the greater curvature than on the lesser curvature, and no visible lesions.. The same previously-described picture was observed in the stomachs of groups II, III &IV at T0 and also at T7 in groups III &IV. In our endoscopic evaluation gastric mucosal injuries including five endoscopic severity scores have been reported rapidly at T7 in group II, and maximal damage appeared within T7 to T14in group II including one perforated ulcer in pylorus that causing death of the at T11, also, in group II, the endoscopic severity scores of 3 and 4 at T14 were 50% and 25%. Both esomeprazole and misoprostol co-treatment recorded gastric protection in T7 in groups III and IV and the stomach mucosa was entirely normal, so esomeprazole with endoscopic severity score of 0% in both groups, while endoscopic severity scores of 3 and 4 at T 14 were 20% and 0% respectively in group III and 60% and 0% respectively in group IV. The site of gastric lesions in meloxicam treated groups (II, III, IV) were the antrum, and the lesser curvature and frequently the pylorus.

Table 3: Means and SE of biochemical parameters in control and experimental group at five time points

Items		Group I (control)	Experimental groups			P-value
			group II (Meloxicam)	group III (Melox.+ Esmop.)	group IV (Melo+ Misop.)	
Gastrin (ng/l)	Day 0	29.33 ± 2.517	28.00 ± 5.568	27.67 ± 3.512	28.33 ± 2.082	0.949
	Day 3	30.67 ± 2.082^{b}	39.00 ± 3.606^{a}	29.33 ± 4.041^{b}	33.33 ± 3.512^{ab}	0.034
	Day 7	30.67 ± 3.512^{b}	147.0 ± 18.73^{a}	37.90 ± 3.381^{b}	39.00 ± 3.606^{b}	0.000
	Day 10	30.00 ± 2.646^{c}	265.3 ± 46.44^{a}	74.33 ± 2.517^{b}	84.00 ± 4.000^{b}	0.000
	Day 14	28.67 ± 4.041^{c}	379.5 ± 53.50^{a}	106.7 ± 7.024^{b}	111.3 ± 13.38^{b}	0.000
IL1B (Pg/ml)	Day 0	401.7 ± 17.95	395.3 ± 68.19	407.3 ± 30.99	399.3 ± 60.93	0.992
	Day 3	397.0 ± 59.27	455.3 ± 87.65	420.3 ± 62.85	438.0 ± 66.34	0.769
	Day 7	405.0 ± 34.39	471.0 ± 72.63	441.3 ± 18.93	429.3 ± 35.92	0.399
	Day 10	393.3 ± 60.21^{b}	576.3 ± 46.80^{a}	495.3 ± 27.10^{a}	520.7 ± 51.73^{a}	0.010
	Day 14	406.7 ± 62.74^{b}	643.0 ± 44.00^{a}	569.3 ± 40.15^{a}	609.7 ± 34.82^{a}	0.001
TNF-α (Pg/ml)	Day 0	13.67 ± 2.517	13.37 ± 2.219	13.33 ± 1.528	13.73 ± 2.013	0.993
	Day 3	12.83 ± 1.041^{b}	19.67 ± 2.930^{a}	16.50 ± 2.179^{ab}	15.33 ± 2.082^{b}	0.028
	Day 7	13.00 ± 2.000^{c}	68.00 ± 5.568^{a}	31.00 ± 3.606^{b}	28.80 ± 1.992^{b}	0.000
	Day 10	13.83 ± 2.255^{c}	89.67 ± 8.505^{a}	53.67 ± 8.145^{b}	55.27 ± 9.296^{b}	0.000
	Day 14	13.50 ± 2.646^{c}	95.33 ± 15.50^{a}	69.00 ± 12.29^{b}	82.00 ± 8.718^{ab}	0.000
Total protein (gm/dl)	Day 0	6.693 ± 0.466	6.767 ± 0.451	6.667 ± 1.193	6.870 ± 0.365	0.984
	Day 3	6.650 ± 0.797	6.780 ± 0.381	6.557 ± 0.851	6.497 ± 0.592	0.959
	Day 7	6.557 ± 0.522	6.200 ± 0.346	6.300 ± 0.400	6.193 ± 0.681	0.796
	Day 10	6.563 ± 0.566	5.220 ± 0.697	5.540 ± 0.535	5.713 ± 0.738	0.142
	Day 14	6.870 ± 0.552^{a}	5.017 ± 0.401^{b}	5.310 ± 0.332^{b}	5.383 ± 0.798^{b}	0.013
Albumin (gm/dl)	Day 0	4.067 ± 0.462	4.137 ± 0.412	4.133 ± 0.451	4.083 ± 0.284	0.995
	Day 3	4.097 ± 0.663	3.967 ± 0.252	4.067 ± 0.232	4.167 ± 0.451	0.953
	Day 7	4.093 ± 0.388^{a}	3.033 ± 0.351^{b}	3.720 ± 0.464^{ab}	3.900 ± 0.361^{a}	0.048
	Day 10	4.037 ± 0.215^{a}	2.490 ± 0.429^{b}	3.233 ± 0.603^{ab}	3.367 ± 0.404^{a}	0.016
	Day 14	4.100 ± 0.339^{a}	2.533 ± 0.126^{b}	2.883 ± 0.340^{b}	3.063 ± 0.220^{b}	0.001

Table 4: Endoscopic severity scoring of gastropathy in examined dogs.

Time points	Grade *	Group I	Group II	Group III	Group IV
0 day	0	(5/5) 100%	(5/5)100%	(5/5)100%	(5/5)100%
	1	(0/5) 0%	(0/5)0%	(0/5)0%	(0/5)0%
	2	(0/5)0%	(0/5)0%	(0/5)0%	(0/5)0%
	3	(0/5)0%	(0/5)0%	(0/5) 0%	(0/5) 0%
	4	(0/5) 0%	(0/5) 0%	(0/5) 0%	(0/5) 0%
7 day	0	(5/5)100%	(1/5) 20%	(5/5) 100%	(5/5) 100%
	1	(0/5) 0%	(1/5) 20%	(0/5) 0%	(0/5) 0%
	2	(0/5) 0%	(1/5) 20%	(0/5) 0%	(0/5) 0%
	3	(0/5) 0%	(1/5) 20%	(0/5) 0%	(0/5) 0%
	4	(0/5) 0%	(1/5) 20%	(0/5) 0%	(0/5) 0%
14 day	0	(5/5) 100%	(0/4) 0%	(1/5) 20%	(0/5) 0%
	1	(0/5) 0%	(0/4) 0%	(2/5) 40%	(1/5) 20%
	2	(0/5) 0%	(1/4) 25%	(1/5) 20%	(1/5) 20%
	3	(0/5) 0%	(2/4) 50%	(1/5)20%	(3/5) 60%
	4	(0/5) 0%	(1/4) 25%	(0/5) 0%	(0/5) 0%

*Grade: endoscopic severity scoring, stomach with no visible lesions is scored as 0; a stomach with a few submucosal petechia but no visible defects in the mucosa is scored as 1, a stomach with few erosions is scored as 2, stomach with extensive areas of erosions is scored as 2, and stomach with ulcer of any size is scored as 4

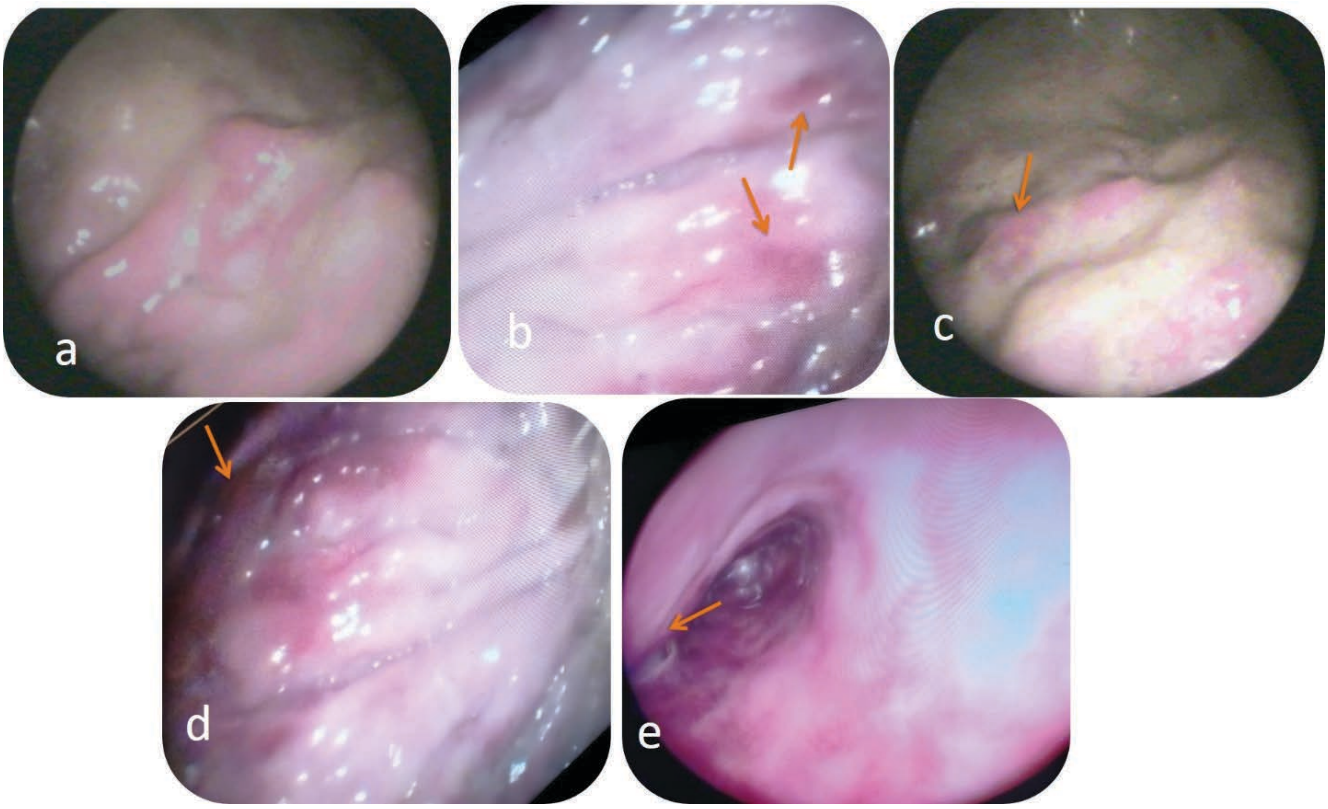

Figure 1: Endoscopic view of gastric mucosa, normal rugal folds of the stomach with no visible lesion (a, score 0), gastric mucosa with multiple petechie (b, score 1), gastric mucosa with few erosions (c, score 2), gastric mucosa with extensive erosions (d, score 3), endoscopic view of pyloric ulcer(e, score 4),

Discussion

NSAIDs are often prescribed only for short-term use in veterinary practice because of the incidence and severity of side effects with prolonged use. However, there is little information in the veterinary literature about long-term use of meloxicam (more than seven days). Gastroprotectants are widely used by veterinarians for the treatment of gastroduodenal mucosal injuries in dogs and cats. This study performed to diagnose gastropathy in dogs caused by 14-day administration, by different methods (clinical, haemato-biochemical, endoscopic, post mortem and histopathological examination).

Regarding vital signs, no remarkable changes were recorded in body temperature, pulse, and respiratory rates similarly (10,11). Except 1 dog in group II, the dog was febrile, tachycardic and tachypneic at T10 and hypothermic at T11 owing to peritonitis caused by perforated gastric ulcer similar to previous reports (9,24).

Inappetence to anorexia, abdominal pain, hematemesis, melena, weakness, emaciation which were recorded in some dogs in experimental groups were similar to previously reported studies (9-11) and in contrast to Eskafian et al. (23). Death in one dog in group II is due to peritonitis resulted from a perforated gastric ulcer (22).

The significant decrease in Hb conc., RBCs and PCV% in group II at T10and the significant decrease at T14 recorded in the three experimental groups (II, III &IV) could be attributed to the adverse effect of NSAID that causes ulceration in the gastric wall, blood loss and anemia, this result coincided with Enberg et al., (9,11).On the other hand, Dobre et al., (24) stated that the preparations of the non-steroidal anti-inflammatory drug used in dogs do not cause obvious hematological changes.

The significant increase in WBCs recorded at T10 and T14 in groups II, III and IV could be attributed to response to the inflammatory reaction in the gastric wall that occurred as a result of the destruction of the bicarbonate layer of the mucosa after inhibition of prostaglandin synthesis this result was in keeping with Elfadadny et al., (11) and disagreed with Enberg et al., (9,24). In group II, the significant increase in neutrophil% at T10

and T14 owing to sepsis resulting from ulcer formation, perforation and peritonitis. This result was agreed with Enberg et al., (9,25) who revealed that the main laboratory finding of piroxicam induced gastric ulceration was neutrophilic leukocytosis. Our results disagreed with Dobre et al., (24).

Gastrin is produced by the G-cells in the antrum of the stomach, and plays a central role in the regulation of gastric acid secretion in humans and animals (26).In our study, Serum gastrin levels in group II increased significantly at T7, T10, and T14, while serum gastrin levels in groups III and IV increased significantly at T10 and T14, consistent with previous studies (10,11,27). The marked increase in serum gastrin concentration in meloxicam treated groups is the result of impairment in the feedback mechanism between gastric acid and antral gastrin secretion. Or due to the direct relationship between the stomach lesions and G cell stimulation (27). So, serum gastrin concentration is used as a biomarker for prediction and monitoring of the severity of meloxicam-induced gastric ulcer (11).

In groups II, III and IV a significant increase in IL1B was recorded at T10 and T14 owing to the damage to the intestinal mucosa that causes microorganisms to enter the lamina propria from the lumen, which triggers an inflammatory response, thus leading to the overproduction of inflammatory cytokines (28).

The highly significant increase in TNFα in groups II, III and IV at T7, T10 and T14 may be owed to gastric damage caused by NSAIDs and leukocyte migration within the gastric microcirculation which triggers the inflammatory response, thus leading to the overproduction of inflammatory cytokines (29).

Endoscopy provides definitive diagnosis for upper gastrointestinal tract disorders, helps confirm diagnosis, and might have therapeutic use (30). Endoscopy can be used to see mucosa of digestive tract when radiography and ultrasonography imaging cannot confirm the diagnosis of such case (31).

Normal endoscopic images recorded in this study were similar to those recorded by Elfadadny et al. (10). In group II at T7 five endoscopic severity scores have been reported equally, This is due to the effect of short-term meloxicam use on gastric mucosa, particularly in the pyloric area.. this result was in agreement with previous reports (10,11,18).

In a previous study, among dogs receiving NSAIDs, six dogs developed gastric lesions on day 7 during endoscopic examination (18). In group II at T14 the endoscopic severity scores of grades 3 and 4 at T14 were 50% and 25% respectively. This result is due to the effect of long-term use of meloxicam on gastric mucosa and submucosa and in some cases musculosa (11).

In group III at T14, the endoscopic severity scores of grades 3 and 4 were 20% and 0% respectively. This is due to the protective and therapeutic action of esomeprazole (15). In group IV at T14, the endoscopic severity scores of grades 3 and 4 were 60% and 0% respectively. This result is due to the cytoprotective action of misoprostol as previous reports (16, 32). Misoprostol co-administered with meloxicam for 14 days prevented a grade 4 endoscopic severity score, but the endoscopic severity score of grades 3 was 60%. So, esomeprazole is superior and more potent to control meloxicam-inducing gastropathy than misoprostol.

Conclusion

This study provides further confirmation of the association between meloxicam use and gastropathy. Endoscopic findings of meloxicam-induced gastropathy are diverse, including gastric mucosal erosions, hemorrhage and ulcers. Giving either esomeprazole or misoprostol concurrently with meloxicam substantially reduces the risk of ulceration. Esomeprazole is more effective than misoprostol at controlling long-term meloxicam-induced gastropathy in dogs

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References

1. Maguilnik I, Neumann WL, Sonnenberg A, Genta RM. Reactive gastropathy is associated with inflammatory conditions throughout the gastrointestinal tract. Alimentary Pharmacology and Therapeutics. 2012; 36(8):736–43.

2. Laine L. Nonsteroidal anti-inflammatory drug gastropathy, Gastrointest Endosc Clin N Am., 1996 Jul; 6(3):489–504.

3. Meddings JB, D Kirk, Olson ME. "Non-invasive detection of non-steroidal anti-Inflammatory drug-induced gastropathy in dogs." Am. J. Of Vet. Res.56.8 (1995): 977–81.

4. Brown SA. Renal effects of nonsteroidal anti-inflammatory drugs, in Kirk RW (ed): Current Vet. Therapy X. Philadelphia, P.A, Saunders,1989; pp 1158–61.

5. Schmidt H. Efficacy and safety of meloxicam in the control of peri-operative pain in the dog. Proceedings of the Recent Advances in Non-Steroidal Anti-Inflammatory Therapy in Small Animals Symposium,1999 ;Paris, France, June, pp 71–4.

6. Engelhardt G, Bogel R, Schnitzler CHR, Utzman R. Meloxicam: Influence on arachidonic acid metabolism. Part II.Invivo findings, Biochem. Pharmacol.,1996; 51, 29–38.

7. Van Ryn J, Pairet M. Inflammation and NSAIDs: COX-1 and COX-2 and preferential COX-2 inhibition. Proceedings of the Recent Advances in Non-Steroidal Anti-Inflammatory Therapy in Small Anim.Symposium, 1999 ; Paris, France, June, pp 15–21.

8. Bjorkman DJ. Nonsteroidal anti–inflammatory drug–induced gastrointestinal injury. Am. J.Med. Sci , 2006; 101, 25–32.

9. Enberg TB, Braun LD, Kuzma AB. Gastrointestinal perforation in five dogs associated with the administration of meloxicam. J. Vet. Emerg. Crit. Care,2006; 16:34–43.

10. Elfadadny AR, Beder NA, Shamaa A A, Nasr MY. Endoscopy diagnosis and follow up of treatment of experimental gastric ulcer in dogs. Eur. J. of Pharmaceutical and Med. Research, ejpmr, 2018; 5(2), 32–8.

11. Elfadadny A, Mandour AS, Ragab R F, Alsharif K F, Batiha GES, Samir H, Beder, NA.A comparative time-dependent study of hematology, serum gastrin concentrations, and gastroscopic assessment of meloxicam-induced gastric ulceration in dogs.J.of Vet. Intern. Med, 2021; 35(5), 2196–204.

12. Parrah JD, Moulvi BA, Gazi MA, Makhdoomi DM, Athar H, Dar S and Mir AQ .Gastric ulceration in dog: A review, Vet .World 6(7):449-454, doi:10.5455/vetworld.2013.449–54.

13. Forsyth SF, Guilford WG, Lawoko CR. Endoscopic Evaluation of The Gastro-duodenal Mucosa Following Non-Steroidal Anti-Inflammatory Drug Administration. New Zealand Vet. J.,1996; 44: 179–81.

14. Jones SM, Gaier A, Enomoto H, Ishii P, Pilla R, Price J, Tolbert MK.The effect of combined carprofen and omeprazole administration on gastrointestinal permeability and inflammation in dogs. J. Of Vet. Inter. Med., 2020; 34(5), 1886–93.

15. Tolbert MK. Gastroprotective therapy. Vet. Clin.Small Anim.Practice,2021;51(1), 33–41.

16. Johnston SA, Leib MS, Forrester SD, et al. The effect of misoprostol on aspirin-induced gastroduodenal lesions in dogs. J.Vet. Intern. Med.,1995;9:32–8.

17. Grindem CB. Schalm's Vet. Hematol., 6th edition. Editors, 2011; Douglas J. Weiss, K. Jane Wardrop.

18. Fergestad, Marte Ragnhild Ekeland, et al. "Serum concentration of gastrin, cortisoland Creactive protein in a group of Norwegian sled dogs during training and after endurance racing: a prospective cohort study." (2016).

19. Narita T, Sato R, Motoishi K, Tani K, Naito Y, Hara S. The interaction between orally administered non-steroidal anti-inflammatory drugs and prednisolone in healthy dogs.J. of vet. Med. Sci.,2007; 69(4), 353–63.

20. Forsyth SF, Guilford WG, Haslett SJ, et al. Endoscopy of the gastroduodenal mucosa after carprofen, meloxicam and ketoprofen administration in dogs. J. Small Anim. Pract., 1998;39:421–4.

21. Davis MS, Katherine K, Williamson K K. Gastritis and Gastric Ulcers in Working Dogs. Front. Vet. Sci., 2016; 3:30.

22. Cortese M M, Tate J E, Simonsen L, Edelman L, Parashar U D. Reduction in gastroenteritis in United States children and correlation with early rotavirus vaccine uptake from national medical claims databases. Pediatr. Infect. Dis. J., 2010; 29(6): 489–94.

23. Eskafian H, Tabrizi AS, Lari MA. Gastroscopic study of meloxicam, tramadol, and their combined administration on the development of gastric injuries in dogs. Topics in Companion Anim. Med.,2017; 32(3), 109–13.

24. Dobre IR, Alexandru DM, Crivineanu M. STUDY ON CHANGES IN HAEMATOLOGICAL PARAMETERS FOLLOWING ADMINISTRATION OF NSAIDs IN DOGS. Hemoglobin (g/dl) LXV, 2019; 37–41.

25. Talbert A, Thuo N, Karisa J, Chesaro C, Ohuma E, Ignas J, Maitland K. Diarrhoea complicating severe acute malnutrition in Kenyan children: a prospective descriptive study of risk factors and outcome. PloS one, 2012; 7(6): e38321.

26. Stepan V, Sugano K, Yamada T, Park J, Dickinson C J. Gastrin biosynthesis in canine G cells. Amer.J.of Physiology-Gastrointestinal and Liver Physiol.,2002;282(5), G766–5.

27. García-Sancho M, Rodríguez-Franco F, Sainz Á, Rodríguez A, Silván G, Illera JC. Serum gastrin in canine chronic lymphocytic-plasmacytic enteritis. Can. Vet. J.,2005; 46(7): 630.

28. Zhao H, Wang Y, Liu S, Yu Z, Xu Y, Lu Q, Zhao Y. Dynamic Monitoring of Cross-Bred Dogs for Translational Res. In Ulcerative Colitis, 2020.

29. Zou Q, Zhang X, Liu X, Li Y, Tan Q, Dan Q, Liu Z. Ficus carica polysaccharide attenuates DSS-induced ulcerative colitis in C57BL/6 mice. Food & function, 2020; 11(7), 6666–79.

30. Deni Noviana1, Afidatunnisa k, Syafikriatillah AM, Gunanti F1, Zaenab C.Diagnostic imaging and endoscopy of the schnauzer dog with upper gastrointestinal tract disorders. Indonesian J. Of Vet.Sci.,2017; 11(1):1–5.

31. Moore LE. The advantages and disadvantages of endoscopy. J. Clin. Technol. Small Anim. Pract.2003;18 (4):250–3.

32. Lascelles B, Duncan XJ, Michael McFarland, Heather Swann. Guidelines for safe and effective use of NSAIDs in dogs." *Veterinary Therapeutics* 6.3 (2005): 237.