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Study on effect of pantoprazole and ranitidine in canine gastritis

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Abstract
The study was conducted for comparative assessment of Clinical-haemato-biochemical parameters and comparative therapeutic evaluation of the efficacy of PPI (Pantoprazole), and H_2- blocker (Ranitidine) in clinical cases of Canine Gastritis. Six healthy and twelve gastritis affected dogs were selected for the study based on clinical observations, Hemato-biochemical parameters. The significant Hemato-biochemical alterations included increased hematocrit, PCV, TLC, Neutrophil, Monocytes, and Eosinophils, an increase in serum Histamine and decreased Gastrin levels in gastritis affected dogs. On comparative evaluation, Pantoprazole treated group showed significant ($P<0.05$) changes in Hemato-biochemical parameters on day 5 of therapy as compared to Ranitidine treated groups.

Keywords: Pantoprazole, ranitidine, histamine, gastrin, gastritis

Introduction
The gastric disease is usually the result of inflammation, ulceration, neoplasia, or obstruction. Clinical manifestations include vomiting, hematemesis, melena, retching, belching, hyper salivation, abdominal distention, abdominal pain, and weight loss. Considering gastric disease as a group of clinical syndromes, the clinical approach should be based on etiology, pathology, and clinical presentation [1].

Acute gastritis in canines is characterized by sudden onset of vomiting and PMN infiltration of the mucosa of the antrum and body, which is related to gastric mucosal injury or inflammation. The cause is often inferred from the clinical history, but the diagnosis is seldom confirmed by biopsy and the treatment is mainly symptomatic and supportive, rather than disease-specific [2]. Generally, acute gastritis is related to the long-term intake of some drugs (e.g. non-steroidal anti-inflammatory drugs such as NSAIDs, mechanical trauma, systemic infections, severe stress (e.g. trauma, surgery), ischemia and shock. There is minute evidence to support a role for any infectious agent in acute gastritis [3]. Gastric foreign bodies are very common in dogs and are likely to be seen in younger animals [4].

Gastritis is a common finding in dogs, with 35% of dogs investigated for chronic vomiting and 26-48% of asymptomatic dogs affected. Chronic Gastritis is defined as the presence of intermittent vomiting for more than 1-2 weeks [5]. A diagnosis of chronic gastritis is based on histologic examination of gastric biopsies and it is usually sub classified according to histopathological changes and etiology [6]. Physical damage to the gastric mucosa, impairment of mucosal defense, chemical changes in the mucosa and its repair process is the pathophysiological factors of gastric ulceration [7]. In dogs, gastric ulceration is usually associated with the ingestion of a wide range of materials such as abrasive foods, household chemicals, common garden and woodland plants, and items of clothing or household decorations. Mechanical abrasion ulceration is generally shallow and transient, completely healing after a few hours [8].

The most effective treatment for canine gastritis is focussed on a specifically identified cause (e.g. antiparasitic agents, surgical removal of a gastrinoma, discontinuation of an offending drug, removal of an inciting allergen). In addition to specific treatments, there are a large number of agents that can be used in a nonspecific manner, all focussed toward the relief of gastritis and its symptoms. The suitable choice of medication is based on knowledge of the derangement most likely underlying the symptoms (e.g. increased gastric acidity in uremic gastritis, gastric hypomotility in bilious vomiting syndrome) and an understanding of the mechanism of action for each drug.

Materials and Methods

Experiment design

The present study was conducted on six clinically healthy dogs and twelve dogs showing symptoms of gastritis irrespective of age and sex which were divided into three groups.

Group 1: Healthy Dogs: (n=6) were having a normal appetite, no history of vomiting, melena, and abdominal pain. Blood sampling was done on the day of presentation.

Group 2: Pantoprazole treated Dogs (n=6) were showing anorexia or inappetence, vomiting, melena, abdominal pain on the day of the presentation. Blood sampling was done on the day of presentation.

Group 3: Ranitidine treated Dogs (n=6) were showing anorexia or inappetence, vomiting, melena, abdominal pain on the day of the presentation. Blood sampling was done on the day of the presentation.

(No. of dogs = 18)	Health status	Therapeutic strategy
I	Healthy dogs(6)	T0=X
II	Diseased dog (6)	T1= Pantoprazole (@ 1mg/kg BW IV OD) x 5 days
III	Diseased dog (6)	T2= Ranitidine (@1mg/kg BW IV TID)x 5 days

Standard therapy

All the diseased dogs were treated with the same antibiotic, antiemetic and fluid therapy.

Clinical observations: The important clinical parameters of all the dogs were recorded in the form of questionnaire i.e. status of appetite (inappetence/anorexia), vomiting, hematemesis, melena and abdominal pain. For hematological parameters, 3ml blood was collected aseptically from the saphenous/ cephalic vein of each dog in EDTA vials. Samples were taken on the day of the presentation (day 0). Hematological estimation was conducted immediately after the blood collection with a hematology cell counter. Samples for serum separation were kept for one hour and then centrifuged at 3000 rpm for 10 minutes to separate plasma and serum.

The separated samples were stored at -20 °C until the estimation. Various biochemical parameters were estimated using semi-automatic clinical chemistry analyzer with ready to use kits from Coral, Tulip Diagnostic Limited. Gastrin and Histamine levels were estimated by ELISA method using Canine specific ELISA Kit from Genxbio Health Sciences Pvt. Ltd. The following parameters were estimated: Hemoglobin (Hb), Packed cell volume (PCV), Total erythrocyte count (TEC), Total leukocyte count (TLC), Differential leukocyte count (DLC), Blood urea nitrogen (BUN), Creatinine, Total plasma proteins, Histamine and Gastrin. The statistical analysis of the data was done using a software package for social sciences (SPSS) version 20.0. One way analysis of variance (ANOVA) and Tukey's post hoc testing at the $P<0.05$ level of significance.

Results and Discussion

Based on clinical observation and history, all six healthy control dogs were having normal appetite, no history of vomiting, melena and abdominal pain while all the twelve diseased dogs were showing anorexia or inappetance, vomiting (with blood in gastric contents (n=3), gastric contents with bile (n=1) and only gastric contents (n=11), melena (n=3), abdominal pain (n=9) on the day of the presentation are shown in table 1.

Table 1: Clinical observation of healthy control and diseased dogs

Groups		Clinical signs and symptoms				
	Anorexia	Vomiting			Melena	Abdominal pain
		Gastric contents with blood	Gastric contents with bile	Gastric contents		
Group I (n=6)	Absent	Absent	Absent	Absent	Absent	Absent
Group II (n=6)	5	2	1	6	2	4
Group III (n=6)	4	1	-	5	1	5

Pathological lesions due to various disorders of the upper gastrointestinal tract are frequently seen in dogs because of their habit, nature of eating, diet, and habitat [9]. Gastritis-Inflammation of the stomach is a frequently cited differential yet rarely characterized diagnosis in cases of canine anorexia and vomiting [10].

Canine gastritis is categorized and graded subjectively according to the nature of the predominant cellular infiltrate and the presence of architectural abnormalities [5].

Mean±SE values of various hematological parameters of healthy control and diseased dogs on the day of the presentation are shown in table 2. In Group I (Healthy control) dogs, hemoglobin level (Mean±SE) was 11.68±0.22g/dl. The Mean±SE value of PCV was 36.39±0.25%. The Mean±SE value of TEC was 5.23±0.08 $\times 10^6$/µl. The Mean±SE value of TLC was 9.38±0.38$\times 10^3$/µl. The Neutrophil's values (Mean±SE) were 71.17±1.19%. The Mean±SE values of Lymphocytes were 27.00±1.06%. The Mean±SE values of Monocytes were 1.17±0.31%. The Mean±SE values of Eosinophils were 0.83±0.31%. The Mean±SE values of Basophils were 0.00±0.00%.

In Group II (T1 = Pantoprazole treated) dogs, Hemoglobin level Mean±SE was 14.87±0.40 g/dl, while on day 5 of therapy Hb level was 11.27±0.16g/dl. The Mean±SE value of PCV was 41.02±0.35% on day presentation, while on day 5 of therapy PCV value was 40.00±0.48 %. The Mean±SE TEC value was 6.47±0.28$\times 10^6$/µl on the day of the presentation, while on the day 5 of therapy TEC value was 5.43±0.18$\times 10^6$/µl. The Mean±SE TLC value was 13.63±0.59$\times 10^3$/µl on the day of the presentation, while on day 5 of therapy TLC value was 11.91±0.23$\times 10^3$/µl. The Mean±SE values of Neutrophils were 77.50±1.18% on the day of the presentation, while on the day 5 of therapy was 71.83±2.12%. The Mean±SE values of Lymphocytes on the day of the presentation, and day 5 of therapy were 27.00±1.06%, and 27.00±1.06% respectively. The Mean±SE values of Monocytes on the day of the presentation and day 5 of therapy were 0.67±0.21% and 1.00±0.26% respectively. The Mean±SE values of Eosinophils on the day of the presentation, day 5 of therapy were 0.67±0.21%, and 0.83±0.17% respectively. The Mean±SE values of Basophils on the day of the presentation and day 5 of therapy were

0.17±0.17 %, and 0.00±0.00% respectively.

In Group III (T2= Ranitidine treated) dogs, hemoglobin level Mean±SE was 15.31±0.54g/dl on the day of the presentation, while on day 5 of therapy Hb levels were 11.89±0.28g/dl. The Mean±SE value of PCV was 41.44±0.61% on the day the presentation while on day 5 of therapy PCV value was 39.42±0.50%. The Mean±SE TEC value was $5.94\pm0.25\times10^6$/µl on the day of the presentation, while on day 5 of therapy TEC value was $5.11\pm0.08\times10^6$/µl. The Mean±SE TLC value was $12.88\pm0.46\times10^3$/µl on the day of the presentation while on day 5 of therapy TLC value was $10.53\pm0.35\times10^3$/µl. The Mean±SE values of Neutrophils on the day of the presentation and day 5 of therapy were 77.00±1.29, and 70.17±0.87% respectively. The Mean±SE values of Lymphocytes on the day of the presentation and day5 of therapy were 18.00±1.86% and 19.83±1.17% respectively. The Mean±SE values of Monocytes on the day of the presentation and day 5 of therapy were 0.67±0.21% and 0.83±0.31% respectively. The Mean±SE values of Eosinophils on the day of the presentation and day 5 of therapy were 0.83±0.48% and 0.67±0.33% respectively. No basophils were found in this group. With the above data, the Mean±SE values of Hb, TEC, TLC and Neutrophil count in diseased dogs were significantly ($P<0.05$) higher on day of the presentation i.e. day 0 than the healthy control dogs. And on day 5 of therapy in both group I and group II the values of Hb, TEC, TLC, and Neutrophil count were all most similar to the healthy control group.

Hemoconcentration as a consequence of dehydration due to vomiting may occur in cases of gastritis [11, 12]. Hematocrit may decrease in association with severe gastric erosions and ulcer disease due to acute or chronic blood loss. Microcytic and hypochromic anemia also reported in different studies [13]. There was no statistically significant difference reported in TLC and DLC values in the present study [14]. Stanton and Bright, 1989 also reported the normal leukogram in dogs with gastric affections. However, marked neutrophilia with a left shift was recorded in 29 dogs affected with gastritis and 32 of 40 dogs had non- regenerative normocytic/normochromic anemia. Anemia (hematocrit <0•37) was found in 34(41%) dogs with gastric mucosa lesions. Anemia occurred more frequently in dogs with a long duration of clinical signs than dogs with short duration of signs [15].

Table 2: Mean±SE values of Haematological parameters of Healthy control (Group I) and Diseased dogs (Group II, III)

Haematological parameters	Group I (n=6)	Group II (n=6) Pantoprazole treated group		Group III (n=6) Ranitidine treated group	
		Day 0	Day 5	Day 0	Day 5
Haemoglobin (g/dl)	11.68±0.22	14.87±0.40	11.27±0.16	15.31±0.54	11.89±0.28**
TEC (10^6/µl)	5.23±0.08	6.47±0.28	5.43±0.18	5.94±0.25	5.11±0.08*
PCV (%)	36.39±0.25	41.02±0.35	40.00±0.48	41.44±0.61	39.42±0.50
TLC (10^3/µl)	9.38±0.38	13.63±0.59	11.60±0.57	12.88±0.46	10.53±0.35**
DLC					
Neutrophils (%)	71.17±1.19	77.50±1.18	71.83±2.12	77.00±1.29	70.17±0.87*
Lymphocyte (%)	27.00±1.06	26.17±1.28	27.00±1.06	18.00±1.86	19.83±1.17
Eosinophils (%)	0.83±0.31	0.67±0.21	0.83±0.17	0.83±0.48	0.67±0.33
Basophils (%)	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Monocyte (%)	1.17±0.31	0.66±0.32	1.00±0.26	0.67±0.21	0.83±0.31

Means with different superscripts vary significantly ($P<0.05$)

Mean±SE values of various biochemical parameters of healthy control and diseased dogs on the day of the presentation are shown in table 3.

Comparative analysis of the study revealed that there were no significant differences in the Creatinine, BUN, SGPT, Total Protein and Albumin values on day 0 and day 5 of therapy in both Group 2 and Group 3. Comparative analysis of the study revealed that there were significant ($P<0.05$) differences in the Histamine and Gastrin-17 parameters on day 0 and day 5 of therapy in both the treatment groups but the Pantoprazole treated group show highly significant ($P<0.05$) differences in the Histamine and Gastrin-17 parameters on day 0 and day 5 of therapy i.e. The Serum Histamine value on day 5 of therapy was significantly ($P<0.05$) lower than the day 0 value of serum Histamine.

The Serum Gastrin-17 value on day 5 of therapy was significantly ($P<0.05$) higher than the day 0 value of serum Gastrin-17. Ranitidine with Pantoprazole has the notable property of suppressing gastric acid secretion and raise intragastric pH in dogs which leads to increased plasma gastrin concentration [16, 17, 18].

In an in vitro study conducted by Robinson and Horn, the inhibition rates of gastric H/K Adenosine triphosphatase with Pantoprazole were studied, and it was reported that the in vitro inhibition of Pantoprazole could inhibit 50% of the enzyme at the end of 45 min. The results of this in vitro study are comparable with the action of Pantoprazole found in our study [19]. Uchiyama *et al*. 1999, also reported that Pantoprazole was the most potent histamine-stimulated gastric acid secretion inhibitor [20].

The Ranitidine is the most potent H_2 antagonist which suppresses Hcl secretion through competitive inhibition of the parietal cell histamine receptors. Its inhibition of acid secretion peaks at 90% within 1.5 hours, and 50% inhibition of acid secretion lasts about 4 hours after administration [7].

Table 3: Mean±SE values of Biochemical Parameters in Healthy Control (Group I) and Diseased Dogs (Group II, III)

Biochemical parameters	Group I (n=6)	Group II (n=6) Pantoprazole treated group		Group III (n=6) Ranitidine treated group	
		Day 0	Day 5	Day 0	Day 5
SGPT (IU/L)	32.83±1.92	33.00±1.65	31.00±0.73	34.17±1.80	31.00±1.57
BUN (mg/dl)	20.33±1.09	23.81±0.40	24.67±0.33	24.83±0.48	24.00±0.26
Creatinine (mg/dl)	1.01±0.07	1.03±0.08	0.90±0.05	1.28±0.10	1.13±0.10
Total Protein (g/dl)	6.56±0.17	5.35±0.17	5.70±0.11	5.23±0.22	5.71±0.10
Albumin (g/dl)	3.21±0.06	2.57±0.02	2.75±0.03	2.53±0.07	2.61±0.07

Histamine (ng/ml)	1.05±0.09	6.98±0.17	2.77±0.07***	6.13±0.10	3.18±0.05**
Gastrin (ng/L)	27.43±0.26	18.78±0.43	32.25±0.42***	21.75±0.29	32.58±0.37**

Means with different superscripts vary significantly (*P<0.05*)

Conclusions

- Vomiting is the cardinal sign of gastritis in dogs.
- Serum Gastrin and Histamine levels can be used as a sensitive biomarker for the serological diagnosis of gastric inflammation.
- Ranitidine and Pantoprazole can act as a potential therapeutic alternative in Veterinary Medicine due to healing rates are consistently higher, irrespective of baseline disease severity.

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