Clinical and Biochemical Studies on the role of Histamine in Gastrointestinal Disorders in Dogs.

Sarwat, M. A.; Rakha, G. H.; El-Mashad, N. E.

Department of Medicine and Infectious Diseases, Faculty of Veterinary Medicine, Cairo University, Giza, 12211.

Abstract

Canine Gastrointestinal Disorders is fairly common encounter in canine practice. Nevertheless, investigations of new underline causes options have been limited. This study carried out for assessing the role of histamine, as a player canine gastrointestinal disorders and adverse food reaction. This is a, controlled Study over a period of 25 months, designed for evaluation the role of histamine in canine gastrointestinal disorders, 16 adult dogs suffering from canine gastrointestinal disorders inclusion criteria were diarrhea, and vomiting which had been present for at least one day. Animals showed good responses to intramuscular injection of H1R antagonist; pheniramine maleate and consequently the gastrointestinal disorders diminished, dogs were tolerated the treatment, and there were no adverse effects. Therefore, H1R antagonist may be an alternative treatment option for patients with canine gastrointestinal disorders. The success rate seems to be a promising option for the future treatment of canine gastrointestinal disorders in dogs. The use of H1R antagonists will provide an additional choice beside H2R blockers for the therapeutic options to treat GIT disorders in dogs. Results obtained in the present study showed that serum histamine level as well as symptoms had been decreased significantly after treatment.

Keywords: histamine, dog, gastrointestinal disorder, H1R antagonist, pheniramine maleate.

Introduction

Histamine is short-acting endogenous amine, which is widely allocated throughout the body, is synthesized by histidine decarboxylase (HDC), which decarboxylates the semi essential amino acid L-histidine. Originally uncovered at the beginning of the 20th century, histamine was first chemically synthesized by Windaus and Vogt in 1907, in 1910, the first biological functions of histamine were reported by Barger, and Dale, (1910); Dale, and Laidlaw, (1910). They recognized that histamine had the ability to mimic smooth muscle—stimulating and vasodepressor action observed during anaphylaxis. Jia-Liu, et al., (2014) stated that histamine was isolated from liver and lung tissue in 1927 before purification from other tissues succeeded and gave histamine its name based on the Greek word histos, which means tissue. Jia-Liu, et al., (2014) reported that histamine, 2-[4-imidazoyl] ethylamine, is an important mediator of anaphylactic reactions. Histamine is a decarboxylation product of histidine and is released from mast cells, basophiles, and a number of other a great many other various other cell types, including normal and malignant lymphocytes. Histamine is a potent of several biologic reactions and is one of the main mediators of allergic reactions. It can also stimulate and generate acute and chronic hypersensitive responses Koyama, et al., (2009).

Histamine exerts their actions via binding to four different G necessary protein coupled receptors (H1, H2, H3, and H4) through the entire body (Parsons and Ganellin, 2006). Histamine is produced by a multitude of cell types and is involved with many physiological functions, including cellular proliferation and differentiation, hematopoiesis, embryonic development, regeneration, and wound healing (Jutel 2002; Schneider, et al., 2002; Akdis and Blaser, 2003; MacGlashan, 2003, Dy-M and Schneider 2004).

This study was carried out for assessing the histamine in canine gastrointestinal disorders.
**Material and methods**

Control group included (C Gp, n=8); 6 males and 2 females. Breeds are 5 Mongrel, 1 Pit-bull and 1 Labrador retriever; they range from 9 months to 8 years old with an average of 3 year old, while gastrointestinal diseased dogs (GID Gp, n=8); 3 males and 5 females. Breeds are 6 mongrels, 1 Pit-bull and 1 German shepherd. They range from 6 months to 7 years old with an average of 3.5 year old. Physical examination, complete blood count, chemical examination and serum histamine estimation by histamine ELISA test were applied. Drugs given to animals; anti-histaminic, antibiotics, anti-inflammatory, fluid therapy, antidiarrheal, and supplements treatment.

**Trade name** | **Manufacturer** | **Active principle (s)** | **Usage, route, dose and duration**
--- | --- | --- | ---
Avil® | Sanfi-aventis | Pheniramine maleate | 1st generation H1R antagonist, I.M administration of 1.0-1.5 ml/35 kg bwt q 12 hrs.
Augmentine® | GSK | Amoxicillin-clavulenate | Antimicrobial for digestive and respiratory problems, I.M administration of 12.5-25 mg/kg bwt q 6-8 hrs.
Enroxx® | Alex | Enrofloxacin | Antimicrobial for digestive and respiratory problems, I.M administration of 10 mg/kg bwt q 6-8 hrs.
Fucidin® | LEO | Sodium fusidate 20 mg | Antimicrobial for skin problems, topical application twice/day.
Sodium chloride® 0.9% | Almutahedo on pharma | Sodium chloride 9 gm/l (sodium & chloride 154 mmol/l each) | I.V administration of 5-6 ml/min according to fluid deficit and = (Bwt × percent of dehydration × 10) = amount given for the first 5-6 hrs, then maintenance daily dose of 60-120 ml/day according to severity of the case.
Glucose® 5% | Almutahedo on pharma | Anhydrous glucose 50 gm & water upto 1000 ml. | I.V infusion of 8-15 mg/kg bwt every 12 hrs.
Sodium chloride® 0.9% & Glucose® 5% | OTSUKA pharma | Dextrose monohydrate 0.5 gm, Sodium chloride0.9 gmin each 100 ml water + water upto 1000 ml for injection | I.V administration according to fluid deficit and ongoing loss of fluids (vomiting).
Ringer’s solution® | Almutahedo on pharma | NaCl 147.5 mmol/l - KCL 4 mmol/l - CaCL2 2.25 mmol/l - Total CL 156 mmol/l | I.V infusion of 1-1.5 ml/50 kg every 12 hrs.
Flagyl® | Alex/Sanofi-aventis | Metronidazole | Oral administrations of 1 capsule/dog every 6-8 hrs.
Vetalgin® | Intervet | Sodium metamizole | Oral administration of 5ml/dog every 8 hrs as a dietary supplement.
Antinal® | AMOUN | Nifuroxazide | Oral administration of 5ml/dog every 8 hrs as a food supplement.
Multisanistol® | Chemi pharm | Vitamin A, B, C, D, E, Calcium, Ferrous, and Phosphate (43.5mg/5mg) | Oral administration of 5ml/dog every 8 hrs as a dietary supplement.
Immulant® | MEPACO | Echancea dry extract & Nigella sativa oil | Oral administration of 5ml/dog every 8 hrs as a dietary supplement.

**Results and discussion**

Results of histamine values, hematological parameters, biochemical and parameters values in both control group and GIT disorders group are shown in table 1, 2, 3, 4 and graph 1.

**Table (1):** Pulse rate (ppm), respiratory rate/min, body temperature (C), and mucous membrane among different groups

<table>
<thead>
<tr>
<th>Item</th>
<th>Control group (CGp, n=8)</th>
<th>Gastro intestinal group (GIDGp, n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse rate (ppm)</td>
<td>Mean: 122.7, Range: 80 - 139</td>
<td>Mean: 129.1, Range: 78 - 144</td>
</tr>
<tr>
<td>Respiratory rate/min.</td>
<td>Mean: 34.2, Range: 24 - 43</td>
<td>Mean: 38.6, Range: 26 - 44</td>
</tr>
<tr>
<td>Body temperature (C)</td>
<td>Mean: 38.8, Range: 38.5 - 39.0 C</td>
<td>Mean: 38.7, Range: 38.4 - 39.0 C</td>
</tr>
<tr>
<td>Mucous membrane</td>
<td>Salmon Pink color</td>
<td>Pale color</td>
</tr>
</tbody>
</table>
Our results agree with finding of He-SH, et al., (2004); Buhner, et al., (2009), the pathological relevance of increased histamine levels at compromised sites is less well understood in disorders, such as inflammatory bowel disease and irritable bowel syndrome, histamine might negatively or positively influence parasitic or bacterial infections (Banu, et al., 1999; Jutel, et al., 2001; Beghdadi, et al., 2008; Buhner, et al., 2009). Cells of both the innate and adaptive immune response can be regulated by histamine (Jutel, 2002; Akdis and Blaser, 2003).
Amorim et al., (2016) stated that histamine have been documented in humans with chronic GI diseases such as Crohn's disease, ulcerative colitis, irritable colon syndrome and allergic enteropathy (Xie and He, 2006; Thurmond, 2010; Smuda and Bryce, 2011).

Inside the GI tract, histamine is involved in regulation of gastric acid production, muscle motility, and mucosal ion transport (Sander et al., 2006). Histamine also has a role in mucosal defense and neurotransmission (Peters and Kovacic, 2009).

Sullivant et al., (2016) stated that histamine receptors in the differing sections of the canine gastrointestinal tract will provide additional research opportunities to further explore the role of histamine and its receptors in canine enteropathies, as well as potential therapeutic options. All 4 histamine pains were readily identified.

Amorim et al., 2016; Smuda and Bryce, 2011; Thurmond, 2010 stated that histamine has been shown to have a natural part in many functions of the gastrointestinal (GI) tract, including neurotransmission, visceral nociception, and mucosal defenses (Peters and Kovacic, 2009; Deiteren et al., 2015).

Sander, et al., (2006) mentioned that intestinal epithelial cells might be protected from pathogenic infection because of, histamine signaling epithelial skin cells subjected to histamine resulting in having lower amounts of invasive intracellular pathogens in vitro, which was mediated simply by the H1R. Duan, (2010) suggested that protection of the gastrointestinal mucosa from pathogen invasion might be dependent, in part, on the local concentration of histamine (Feng, et al., 2007; Wu-L, et al., 2007). Low levels of histamine might be protecting, whereas higher levels might be bad for epithelial protection from infection (Ciprandi, et al., 2003; Hou, et al., 2006).

Histamine is a potent signals geber of gastric acid release. Sources of histamine in the GI tract are enterochromaffin-like cells (ECL), mast cells, and neuronal fibres. ECL cells are under both humoral and neurological regulation and are triggered by inflammation in the gastric mucosa (Repka-Ramirez and Baraniuk, 2002; Peters, and Kovacic, 2009; Jadidi-Niaragh, abd Mirshafiey, 2010).

Dogs with IBD have increased GI tract mast cell denseness, and several have high levels of urine N-methyl histamine, a metabolite of histamine (Berghoff et al., 2014). In 2008, the dog H4 receptor was cloned, and PCR techniques were used to distinguish H4 receptor expression in the canine small intestine (Jiang et al., 2008).

Mast cells may get involved in inflammatory processes of the intestine through the release of a variety of inflammatory mediators, such as histamine. (Le, et al., 1995; Winterkamp, 2002; He-SH, et al., 2004; Peters, and Kovacic, 2009; Kumar, and Sharma, 2010; Berghoff, 2011).

The inhibition of H1 receptor activity by the application of two recognized histamine H1 antagonists (triprolidine or mepyramine) reduced the ability of posterior hypothalamic explants to protect the hippocampus from KA-induced cellular death Panula, et al., (2007), histamine seems to have significant neuroprotective results. It is thus which the increased histamine level and histamine release noticed in both ischemic conditions and hibernation represent a relevant physiological response to neurological stress and anoxia, starting up the opportunity of the therapeutic use of histamine and/or histamine receptor legends’ to treat related clinical conditions Panula, et al., (2007).

Dogs have relatively few adverse results to H1R antagonists when used at appropriate doses; nevertheless, effective clinical response in allergic disorder management is variable.

H2R antagonists such as famotidine and ranitidine are widely used to treat peptic ulcers, and gastrointestinal bleeding in puppies and cats. In humans, H2R antagonists are being used not just for gastroesophageal reflux disease and healing gastric, duodenal, and esophageal ulcers but also in the elimination of gastrointestinal ulcers in critically ill patients.
**Conclusion**

This investigation advocates that H\textsubscript{1}R antagonist; pheniramine maleate and consequently the gastrointestinal disorders diminished, dogs were tolerated the treatment, and there were no adverse effects. Therefore, H\textsubscript{1}R antagonist may be an alternative treatment option for patients with Canine Gastrointestinal Disorders and adverse food reaction (CAF R). Future investigation into the mechanism with controlled clinical studies using a large number of patients will be necessary to provide supporting evidence for this potential treatment. The success rate seems to be a promising option for the future treatment of Canine Gastrointestinal Disorders and adverse food reaction (CAF R) in dogs. The use of H\textsubscript{1}R antagonists will provide an additional choice beside H\textsubscript{2}R blockers for the therapeutic options to treat GIT disorders in dogs. Results obtained in the present study showed that serum histamine level as well as symptoms had been decreased significantly after treatment.

**References**


Feng BS, He SH, Zheng, PY, Wu L, Yang, PC. (2007): Mast cells play a crucial


**Xie Ska, H., He, S., (2007):** Roles of histamine and its receptors in allergic and inflammatory bowel disease. World J Gastroenterol. 11, 2851–2857

**الملخص العربي**

دراسات اكلينيكية وبيوكيمائية على دور الهستامين في أمراض الجهاز الهضمي في الكلاب

مؤمن أحمد ثروت – جمال رخا – ناجى المشد

تعد اضطرابات الجهاز الهضمي ضمن تلك الأمراض الشائعة إلى حد ما في الكلاب. ومع ذلك، فإن البحث عن أسباب جديدة مؤدية لهذه الأمراض أصبح محدودا. وتقوم هذه الدراسة على تقييم دور الهستامين في أمراض الجهاز الهضمي في الكلاب. وقد استغرقت الدراسة حوالي 25 شهرا باستخدام عدد 16 كلبا بالغة تعاني من اضطرابات في الجهاز الهضمي وتتمثل هذه الاضطرابات في حالات إسهال وقيؤ تم تشخيصها لمدة يوم واحد على الأقل. أظهرت الحيوانات استجابات جيدة عند حقنها عضليا بعقار الفينرامين ماليات وهو أحد عقاقير الجيل الأول من مضادات الهستامين. وفي الآونة الأخيرة، حدث تقلص في عدد حالات الاضطرابات الجهاز الهضمي. تقبلت الكلاب العلاج بدون أي أعراض جانبية مع استخدام عقاقير الجيل الأول من مضادات الهستامين علاجا بدلا في حالات اضطرابات الجهاز الهضمي في الكلاب.

وبعد عن ظروف النجاح الذي حدث في الدراسة مؤشرًا قويًا على وجود خيار واعد في المستقبل من مضادات الهستامين متمثلًا في عقاقير الجيل الأول من مضادات الهستامين إلى جانب عقاقير الجيل الثاني من مضادات الهستامين في علاج اضطرابات الجهاز الهضمي في الكلاب.

وقد أظهرت نتائج الدراسة الحالية أن معدلات الهستامين في سيرم الدم وكذلك الأعراض تقلت بشكل ملحوظ في تلك الحالات بعد استخدام علاج الفينرامين ماليات.