Veterinary and Animal Science 10 (2020) 100138

Contents lists available at ScienceDirect

Veterinary and Animal Science

journal homepage: www.elsevier.com/locate/vas

Preliminary comparative serological evaluation of Histamine H2 receptors in dogs with an acute onset of vomiting treated with Ranitidine and healthy dogs

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ARTICLE INFO

Keywords:
Ranitidine
Histamine-2 receptors
Dog
Vomiting

ABSTRACT

Despite the lack of evidence of the ability to suppress gastric acid secretion in dogs, ranitidine (RT) is often used to control clinical signs in dogs with acute vomiting even if the way it happens it is still largely unknown. The aim of this study was thus to evaluate the therapeutic effect of ranitidine on H2 receptors in dogs with acute vomiting. To investigate the RT activity a preliminary study was performed in dogs which underwent gastroscopy analyses, demonstrating that the level of H2R observed in the serum and gastric wall tissue was the same [1.473(1.30; 1.79) ng/ml and 1.498 (1.33; 1.85) ng/ml, respectively]. After that H2R levels in the serum of 22 healthy dogs (Group 1) and in a group of 22 dogs with acute vomiting (Group 2) were compared both before (T0), after 7–10 days (T1) of 2 mg/kg twice a day ranitidine administration and after 11 days since the drug was discontinued (T2). Significant differences ($p < 0.001$) were detected between the level of circulating H2R among Group 1: 0.41 ng/ml (0.28;0.54) and Group 2: 2.27 ng/ml (2.11;2.49) at T0. In Group 2, no difference in the level of H2R was detected in samples collected at T0 compared to those at T1 [T1: 2.32 ng/ml (2.14; 2.49)] and T2 [T2: 2.30 ng/ml (1.99;2.69)]. In Group 2 all patients but one displayed remission of symptoms attributable to inflammatory gastropathy at the first withdrawal (T1: 7–10 days), while at the second withdrawal (T2: after 21 days), remission was detected in all dogs. Our preliminary hypothesis is that the clinical efficacy of ranitidine is related to the greater expression of H2 receptors in patients with acute vomiting. This increased expression may be due to continuous pathological stimulus at the gastric level. Further studies with a wider population are needed to better investigate the activity of RT in dogs with acute onset of vomiting.

Introduction

Ranitidine (RT) is one of the antagonists against H2 histamine receptors (H2R) that clinically decreases gastric acid secretion in human patients (Panula et al., 2015). H2 histamine receptor antagonists (H2RA), also called H2 blockers, impede the action of histamine at the level of H2 histamine receptors (H2R) of parietal cells in the stomach (Marks et al., 2018). They are competitive antagonists of histamine which exert their action through complex mechanisms. Histamine released by Enterochromaffin- like cells (ECL) in the stomach is blocked from binding on parietal cell H2R (which stimulate acid secretion); therefore, other substances that promote acid secretion also through the release of histamine (such as gastrin and acetylcholine) have reduced effects on parietal cells when the H2R are blocked (Tiligada and Ennis, 2018). These actions decrease the basal and meal-stimulated gastric acid secretion (Marks et al., 2018; Panula et al., 2015). In companion animals, there are few studies concerning the mechanism of action and efficacy of ranitidine (Marks et al., 2018). In a study RT is much less effective in increasing gastric pH then famotidine or proton pomp inhibitors in healthy beagle dogs (Bersenas et al., 2005). Moreover, RT seems not to prevent gastroesophageal reflux in anesthetized healthy bitches when compared to metoclopramide and placebo (Favarato et al., 2012). Despite the lack of studies demonstrating its efficacy, RT is anecdotally used to treat nausea and vomiting in dogs or to prevent non-steroidal anti-inflammatory drugs side effects in different settings (intravenously in intensive care, subcutaneously in

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https://doi.org/10.1016/j.vas.2020.100138
Received 9 October 2019; Received in revised form 20 July 2020; Accepted 20 July 2020
Available online 21 July 2020

clinics or prescribed orally for home use) due to its wide maneuverability and safety (Daly and Price, 1983). This preliminary study arises from the interest in better understanding why ranitidine is perceived as effective in patients with acute vomiting. Our hypothesis is that in patients with acute vomiting there could be greater expression and activation of H2 receptors on the gastric mucosa and, therefore, their blockage by RT might justify its clinical efficacy.

In order to accomplish this, a preliminary study was performed to establish the levels of H2 receptors in serum and gastric wall respectively, in a population of dogs that underwent routine gastrointestinal endoscopy.

Subsequently the variation in serum H2R in the acute vomiting group before and after RT administration and in a healthy control group was evaluated.

Materials and methods

Preliminary study

In a preliminary study, endoscopic examination of the gastrointestinal tract was performed in 34 dogs for different clinical reasons: 20 patients with chronic gastro-intestinal symptoms, five dogs with signs of chronic inflammatory colopathy and nine dogs admitted for gastric foreign body ingestion.

The endoscopic investigation and biopsies were performed according to *"Endoscopic, Biopsy, and Histopathologic Guidelines for the Evaluation of Gastrointestinal Inflammation in Companion Animals"* (Washabau et al., 2010). For each dog, four gastric biopsies were performed (two samples collected from the body and two from inside the fundus using biopsy forceps with oval and fenestrated 2.4 mm cups) and 4 ml of whole blood were taken during the usual preoperative screening. The endoscopic investigation and biopsies were performed with the owner's permission. All procedures were carried out exclusively after the written consent was signed by the owner. The H2 receptors level measurement was performed (N = 34) using immunoenzymatic assay and Western Blot assay techniques for both serum and tissue samples. Results were then tested to evaluate correlation and are presented in Table 1.

Concentration of H2R in dog sera - animals and experimental design

Due to the correlation between H2R levels in blood and tissue samples obtained in the preliminary study and to avoid animal suffering, it was decided to evaluate H2R levels in serum samples of the study populations. In this study, 44 dogs were included. For each dog, a blood sample was taken to obtain serum to evaluate the dosage of H2R. All procedures were carried out exclusively after the owner consent form was signed.

In Group 1 (N = 22) healthy dogs were included. They had no history of gastrointestinal disease (vomiting, diarrhea, nausea, anorexia, weight loss), no drugs were administered in the previous 30 days and they resulted clinically healthy on physical examination. They went for the annual check-up screening test (Leishmania or Filaria testing or generic biochemical control analyses). The serum leftovers were taken and stored at –80 °C within 24 h until the analysis was performed.

In Group 2 (N = 22) we included dogs showing signs of acute vomiting (onset within seven days). The following information was collected from each patient: breed, body weight, age, sex and reproductive status, clinical and pharmacological anamnesis and clinical signs. Hematological features were registered when present. As far as the clinical visit and anamnesis are concerned, patients were assigned to one of the following groups:

Light vomiting (A): active subject with dehydration below 4%, less than three episodes of vomiting in 24 h, not anorexic and not in need of hospitalization.

Heavy vomiting (B): depressed subjects, showing signs of dysorexia or anorexia or systemic illness and dehydration above 4% and may be in need of hospitalization (Table 2).

The diagnostic process involved the use of various analyses and techniques to obtain the diagnosis and to subsequently set up the therapy. The dogs included in Group 2 were treated with 2 mg/kg of RT twice a day for 10 days. The treatment was given orally (OS) or intravenously (IV), as prescribed by the veterinarian. When necessary, other drugs were used (Table 2). Before starting the therapy with RT, 2 ml of blood serum were obtained from venipuncture [T0]. Further sera samples were obtained after 7–10 days [T1] and at 21 days [T2], eleven days after the therapy was interrupted. All samples were quickly stored at −80 °C after the collection until the analysis was performed. The follow-up was performed by medical examination at the same time of the blood sample collection in group 2. The absence of gastrointestinal signs in the further 30 days was checked by phone for group 1. All relevant clinical data are listed in Table 2.

H2 immunoenzymatic assay (serum and tissue)

The analyses were carried out using a commercial detection kit (Canine HRH2-ELISA Kit- Elabscience Biotechnology Co.,Ltd). The ELISA test is specific for dog and able of assessing with a satisfactory degree of sensitivity and specificity the concentration of H2 receptors both in serum and in tissue homogenates. The test used to detect the level of Canine Histamine Receptor H2 in serum or tissue, is based on the principle of biotin double-antibody sandwich technology enzyme-linked immunosorbent assay. Standard and Samples were added to the pre-coated wells with objective antibody and streptavidin HRP to form an immune complex. Then the samples were incubated, washed to remove the unbound enzyme and the substrate A and B were added. The final solution turned blue and then changed into yellow because of the effect of the acid. The color depth or light was positively correlated with the concentration of H2R. Intra-assay CV (%) was less than 10% and Inter-assay CV (%) was less than 15% and the sensitivity by this assay was 0.1 ng/ml.

Western Blot assay

To confirm obtained results with the immunoenzymatic assay, a Western Blot procedure was performed for all samples to detect H2R in accordance to the method described by (Boer et al., 2008) using canine polyclonal to HRH2 / Histamine H2 Receptor (Life Spain BioSciences Inc.) (Boer et al., 2008).

Statistical analysis

Data were tested for normality by performing Shapiro-Wilk test. Wilcoxon test was used to compare the level H2 receptors in the gastric wall tissue and in the blood at T0, T1 and T2. For the comparison of the level between sick and healthy dogs the Mann-Whitney U test was applied. Data were summarized with median and interquartile range and p value was set at 0.05 (Statistical software package IBM, SPSS statistic 22).

Table 1.
Biopsy vs Serum H2R concentration (ng/ml). Serum and tissue H2R concentration in dogs (N = 34). Wilcoxon Test, P value = 0.005. Interquartile range H2R serum: (1.30; 0.79). Interquartile range H2R biopsy: (1.33; 1.85).

	H2R serum (ng/ml)	H2R biopsy (ng/ml)
Dogs	N = 34	N = 34
Mean Value	1.473	1.498

Table 2.
Clinical data in referred dogs included in the study ($N = 22$).

ID	Breed	Age (months)	BCS (1–5)	Weight (Kg)	Sex	Vomiting A	Vomiting B	Diagnosis	Therapies	Resolution of symptoms
1	Bichon-frise	14	3	4,5	SF	X		Acute aspecific gastritis	R	Y
2	Mixed breed	96	4	18,4	IF	X		Chronic hepatitis	*R + O*	N
3	Mixed breed	99	5	25,4	NM	X		Leishmaniasis and acute gastritis	*R + O*	Y
4	English setter	94	2	25,2	IM		X	Gastric foreign body, babesios and Leishmaniasis	*R + O*	Y
5	Pug	106	3	8	IM		X	Acute aspecific gastritis	*R + O*	Y
6	American Stafforshire terrier	60	2	24	IF		X	Idiopathic acute hemorrhagic diarrhea syndrome	*R + O*	Y
7	Mixed breed	90	3	28	SF	X		Acute aspecific gastritis	R	Y
8	Mixed breed	11	2	11	IM	X		Acute aspecific gastritis	R	Y
9	Golden retriever	105	4	35,7	IM	x		Urolithiasis	*R + O*	Y
10	Shih-tzu	147	2	6,2	IM	X		Acute aspecific gastritis	*R + O*	Y
11	Labrador retriever	78	4	32	SF	X		Acute aspecific gastritis	R	Y
12	Chihuahua	26	4	3,9	NM	X		Adverse food reaction	R	Y
13	English bulldog	84	4	24	SF	X		Acute aspecific gastritis	R	Y
14	Mixed breed	79	3	7	IM		X	Acute gastritis due to bone ingestion	R	Y
15	Mixed breed	42	3	13,2	IM		X	Adverse food reaction	R	Y
16	Datchshound	72	4	10,2	IM		X	Gastric foreing body	*R + O*	Y
17	Labrador retriever	108	4	40	SF	X		Acute aspecific gastritis	R	Y
18	Jack russel	31	2	4	IF	X		Acute aspecific gastritis	R	Y
19	French bulldog	27	3	15	IM	X		Acute aspecific gastritis	*R + O*	Y
20	Staffordshire bull terrier	42	3	17,5	SF	X		Adverse food reaction	R	Y
21	Chihuahua	99	3	3,2	SF	X		Acute gastritis and pyelonefritis	R	N
22	Labrador retriever	56	3	24,5	SF		X	Acute aspecific gastritis	R	Y

Sex: (mc-mi/fi-fs) NM: neutered male; IM: intact male; IF: intact female; SF: spayed female.
Vomiting: *A* = light-moderate vomiting; *B* = heavy vomiting.
Resolution of symptoms: *Y* = Yes; *N* = no.
Therapy: *R* = Ranitidine 2 mg/kg OS, EV o SC depending on veterinary surgeon's choice; *O*=Other drugs depending on dog's pathology (e.g. prednisone, lattulose, spironolactone, silymarin, ursodeoxycholic acid, allopurinol, imidocarb, ferrous sulfate, maropitant, meloxicam, intravenose fluid therapy, ampicilline, metronidazole).

Results

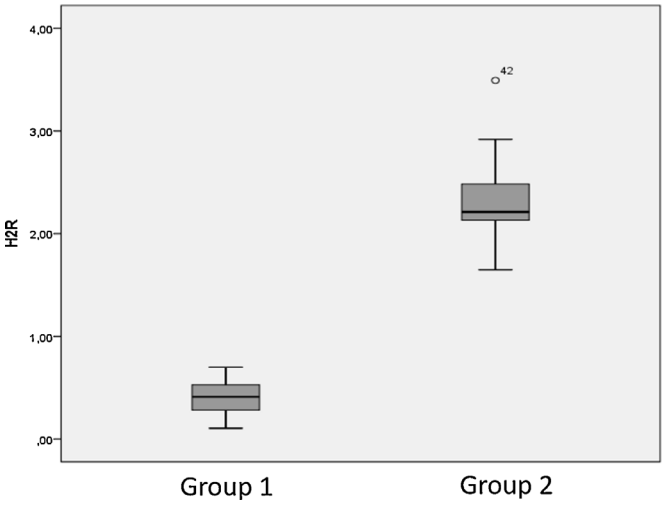
Preliminary study

In the preliminary study, no difference was detected in the level of H2 receptors present in serum and in gastric wall tissue [1.473 (1.30; 1.79) ng/ml and 1.498 (1.33; 1.85) ng/ml] respectively by median and interquartile range (Table 1). These results indicate that concentrations of H2R are statistically significantly equal both in serum (circulating receptors) and in gastric tissue.

The subsequent determinations were therefore performed on the serum. In fact, this result shows that it is possible, in this case, to carry out tests for diagnosis without additional suffering for the dog.

Concentration of H2R in dog sera

Statistical differences were detected between the level of circulating H2R among the healthy dogs [Group 1: 0.41 ng/ml (0.28;0.54)] and sick dogs [Group 2: 2.27 ng/ml(2.11;2.49)] (T0) with $p < 0.001$. (Graph 1). In group 2, no difference in the level of H2 receptors in the serum was detected in the samples collected at T0 compared to the sample collected at T1 [2.32 (2.14; 2.49) ng/ml] and T2 [2.30 (1.99;2.69)] (Table 3). These results indicate that circulating H2R concentrations are statistically significantly different between healthy dogs and dogs with gastroenteric pathology. In particular, dogs with gastroenteric symptoms have a markedly higher concentration of H2 receptors. On the basis of the preliminary study carried out we can also say that the concentration is higher both at the serum level and at the level of the stomach wall. Finally, the results show that there are no significant differences in the concentrations of pathological dog receptors between T0 T1 and T2. This indicates that the ranitidine administration does not change the H2R concentration in this short time.



Graph 1.. Comparison of the average level of H2 receptors found in serum of Group 1 healthy dogs ($N = 22$) versus vomiting dogs Group 2 ($N = 22$) before starting treatment with ranitidine (T0).

Table 3.
Serum H2 levels in dogs tested at T0, T1 and T2 ($N = 22$).

	T0	T1	T2
Dogs	H2R (ng/ml)	H2R (ng/ml)	H2R (ng/ml)
Total	Mean value	Mean value	Mean value
22	2.27 (ng/ml)	2.32 (ng/ml)	2.30 (ng/ml)

Clinical data

Group 1 included 22 healthy subjects who went to various Veterinary Clinics for routine blood tests. None of the dogs developed vomiting or gastrointestinal disease within 30 days after the collection. Group 2 included 22 dogs of various breeds and sizes (included six individuals of mixed breed and four Labrador); sex was equally represented with 11 females (six of which were spayed at the time of the study) and 11 males; median age was 5.9 (1.2–12.2) years old, mean weight was 17.3 kg (4.5–40) and BCS (body condition score) clinically assigned on a 5-point scale at 3.1 (2–5). Fifteen subjects of Group 2 were presented for moderate vomiting (A), while seven patients showed signs of severe vomiting (B). A GI-tract disease as the primary cause of vomiting was proven in 17 dogs, (6/17 in group B) while this could not be affirmed for five of the 22 dogs, which indeed were vomiting for pre-existent conditions as Leishmaniosis (2 of 5), urethral disease (1 of 5), pyelonephritis (1 of 5) and hepatic disease (1 of 5). Among the 17 dogs with proven gastrointestinal conditions, 11 were diagnosed with acute aspecific gastropathy, four with adverse reaction to food, one dog with acute hemorrhagic diarrhea syndrome and one with foreign body ingestion. Thirteen dogs of Group 2 were treated with ranitidine solely, while six received an association of RT plus antiemetic, and 3 RT plus antibiotic (Table 2). In all patients but one (16/17) at the first withdrawal (7–10 days) remission of symptoms attributable to inflammatory gastropathy was noted, while at the second withdrawal (after 21 days) remission was achieved in all subjects.

Discussion

The H2R belong to a large family of G protein-coupled receptors (GPCRs) and play important physiological roles in the regulation of gastric acid secretion, cell differentiation and proliferation, immunological response, and central nervous system functions. H2RA has been widely used to treat acid-related diseases such as peptic ulcer and reflux oesophagitis in human patients (Monczcor and Fernadez, 2016)(In the present study, our results reveal a new perspective regarding the variation in H2R levels in healthy dogs and in those with gastric pathology. The results of the preliminary phase of this study were useful to be able to consider the receptor concentration H2 superimposable on the gastric mucosa and in the serum. However, an objective limit of this evaluation lies in the reduced number of patients and also in the evaluation of only sick patients. Performing biopsies in healthy animals would perhaps be useful, but certainly unethical and therefore it was chosen not to perform them. A first datum worthy of discussion in the study regarding dogs with acute vomiting is the statistically significant difference between H2R levels among healthy dogs and dogs with acute vomiting. We cannot state that the increase of H2 receptors detectable in the serum is the expression of a defined gastric pathology; nevertheless the finding of high values in patients with different acute gastropathies and also in the course of pathologies not primarily gastro-enteric, suggests that histamine can mediate generically gastric reactivity. It would be interesting to be able to make this comparative assessment also in patients with chronic inflammatory gastropathy and in patients with other chronic diseases in which vomiting is a possible symptom. Moreover comparing the data of our preliminary study performed on chronic patients with gastro-enteric inflammation that underwent endoscopy, a higher median value (1.473 ng / ml) than that of healthy patients (0.41 ng / ml) was found. In our opinion, these results are remarkable and should be considered for further studies. The preliminary nature of the data as well as the low number of dogs included in our study constitutes its main limit; this precluded the investigation of a relationship between the number of receptors and variables such as age, breed, sex, or current disease of the animals. Despite these limitations, it would be interesting to evaluate if the value of H2R in the serum could become a possible biomarker of gastric disease. Further studies with a wider population are needed to assess this hypothesis and it might be interesting to evaluate the potential diagnostic role of H2R in patients with chronic gastrointestinal diseases and with severe vomiting of different origin. Obviously in a clinical setting this test could be unnecessary in self-limiting acute vomiting patients. Following the results of our study, the authors hypothesize the possible correlation between the expression of H2R in the stomach during acute pathology and the efficacy of therapeutic treatment with ranitidine. Indeed, we do not rule out that greater H2R expression is positively correlated to the clinical efficacy of RT. This concept deserves further study. In fact we can also consider that the opposite situation occurs: for example the down-regulation of H2R or even gene inactivation. This fact could imply a different expression of the pathology and symptoms and a different patient response to treatment. At the end of the study all included dogs were clinically examined and had a full assessment of their health status. Following treatment with ranitidine, dogs with acute gastric disease had either remitted or recovered. Some studies have shown that dogs do not experience a statistically significant variation of gastric pH when treated with RT or a placebo (Lidbury et al., 2012; Bersenas et al., 2005). Similar results have also been reported regarding the use of ranitidine in cats (Sutalo et al., 2015) and also of famotidine in dogs (Tolbert et al., 2011). For these reasons, given the widespread use of RT and its clinical efficacy in treating nausea in dogs, the authors have attempted to better investigate whether RT interacts with gastric physiology during acute vomiting of various nature. Histamine receptors have previously been shown to enhance delayed hypersensitivity and antibody mediated immune responses. This has been observed in many pathological processes regulating several essential events in experimental animal models, such as allergic conditions and autoimmune diseases, especially in knock-out mice (either H1- or H2-deficient)(Rocklin and Beer, 1983; Quintana et al., 2004). Histamine-mediated signals are largely determined locally by the histamine receptor expression pattern (Boer et al., 2008). The histaminergic pathway leading to acid hyper-secretion to counteract a pH increase in acute vomiting dogs is actively enhanced, but its involvement is only partially responsible (for about 30%) for the aforesaid acidic release; indeed a greater expression of H2R in sick patients might explain the more clinically satisfactory efficacy of ranitidine treatment in this type of patient (Shahid et al., 2009; Shim and Kim, 2017) The over-expression of receptors in patients with acute gastritis could allow RT, which has a higher affinity for H2R only, to have clinical effect without significantly increasing the pH. Bersenas (Bersenas et al., 2005) has shown that RT treatment does not increase gastric pH in dogs. However, the study was performed only on healthy dogs. Although our study is limited and preliminary, ranitidine showed therapeutic effectiveness in 13 dogs when used as the sole treatment of gastropathies (see Table 2). In ten of these subjects the vomiting was of light/moderate severity (A), While in the three animals with severe symptoms (B) and a diagnosis of adverse food reaction that received ranitidine only, a contextual change in dietary habits might have had a determinant role in achieving clinical resolution. If we suppose, on the basis of the bibliography (Bersenas et al., 2005) that in these dogs the RT does not significantly modify the pH, then its clinical effectiveness could also be due to antagonism towards over-represented receptors. Among the seven dogs with severe vomiting (B), the employment of RT alone was effective in three dogs, while in the cases where it was associated with other treatments, therapeutic synergy with RT (see Table 2) cannot be excluded.

The obtained results in the last part of our study showed likelihood to up-regulate the level of H2R in the serum of dogs receiving treatment, although a statistically significant correlation, probably due to the low number of tested dogs, was not shown. However, the up-regulation of H2 (as G protein-coupled receptors) in treated dogs proves the pharmacological efficacy at a molecular level of ranitidine administration. The level of H2R was still high at the time of the second sampling (T2) despite the clinical recovery of the dogs' symptoms. However, the G proteins coupled receptors showed the tendency to

modify their concentration more slowly which might justify this result. It would have been interesting to also evaluate a possible decrease of H2 receptors in the long-term period, unfortunately we could not evaluate all 22 dogs a fourth time since the first withdrawal. The design of this study is subject to some limitations. Unfortunately, the limited number of cases did not allow to perform further statistical analyses (such as comparing the results with age, sex, breed and type of diet). No placebo group was chosen. Moreover, some cases have been treated with medications other than RT, although no drug with interaction with H2R other than RT was taken. Another potential limitation is that we included dogs with multiple diseases. Although it is not proven that the underlying disorder was the only cause of acute vomiting, we decided to include such group of patients because they reflect a category in which RT is commonly used.

Conclusions

In conclusion, the measurement of H2R concentration in the serum of dogs is reliable as it reflects the level of H2R present in the gastric wall. Although the number of patients is small, we found a significant statistic difference between the average level of H2R in healthy dogs and in dogs with primary or secondary gastropathy. This difference could be related to the clinical efficacy that ranitidine has shown during acute vomiting. Therefore we suppose that the clinical effectiveness could also be due to antagonism towards these overrepresented receptors. We cannot say that the quantitative evaluation of H2 receptors has a precise diagnostic and even less therapeutic significance. This hypothesis will be further investigated by carrying out studies with a greater number of patients. Moreover it would be necessary to better define when and if to use receptor research as a non-invasive diagnostic tool during acute and chronic gastro-enteropathy and consequently better define the necessity and efficacy of the treatment with ranitidine.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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