

QUALITATIVE ANALYSIS OF ANATOMOPATHOLOGICAL CHANGES OF GASTRIC MUCOSA DUE TO LONG TERM THERAPY WITH PROTON PUMP INHIBITORS: EXPERIMENTAL STUDIES X CLINICAL STUDIES

Análise qualitativa das alterações anatomopatológicas na mucosa gástrica decorrentes da terapêutica prolongada com inibidores da bomba de prótons: estudos experimentais x estudos clínicos

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ABSTRACT – Introduction: For a few decades the long-term use of proton pump inhibitors has had wide application in the treatment of several gastrointestinal diseases. Since then, however, several studies have called attention to the possible development of anatomical and pathological changes of gastric mucosa, resulting from the long term use of this therapeutic modality. Recent experimental and clinical studies suggest that these changes have connection not only to the development of precancerous lesions, but also of gastric tumors. **Objective:** To present a qualitative analysis of anatomical and pathological changes of gastric mucosa resulting from the long-term use of proton pump inhibitors. **Method:** The headings used were: proton pump inhibitors, precancerous lesions and gastric neoplasms for a non systematic review of the literature, based on Medline, Lillacs and Scielo. Twelve articles were selected from clinical (9) and experimental (3) studies, for qualitative analysis of the results. **Results:** The gastric acid suppression by high doses of proton pump inhibitors induces hypergastrinemia and the consequent emergence of neuroendocrine tumors in animal models. Morphological changes most often found in these experimental studies were: enterochromaffin-like cell hyperplasia, neuroendocrine tumor, atrophy, metaplasia and adenocarcinoma. In the studies in humans, however, despite enterochromaffin-like cell hyperplasia, the other effects, neuroendocrine tumor and gastric atrophy, gastric metaplasia and or adenocarcinoma, were not identified. **Conclusion:** Although it is not possible to say that the long-term treatment with proton pump inhibitors induces the appearance or accelerates the development of gastric cancer in humans, several authors have suggested that prolonged administration of this drug could provoke the development of gastric cancer. Thus, the evidence demonstrated in the animal model as well as the large number of patients who do or will do a long-term treatment with proton pump inhibitors, justifies the maintenance of this important line of research.

HEADINGS - Proton pump inhibitors.
Precancerous conditions. Stomach
Neoplasms.

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RESUMO – Introdução: Há algumas décadas o uso prolongado de inibidores de bomba de prótons tem tido ampla aplicação no tratamento de doenças gastrointestinais. Desde então, entretanto, vários estudos têm alertado para o possível desenvolvimento de alterações anatomopatológicas da mucosa gástrica, decorrentes do uso prolongado desta modalidade terapêutica. Estudos clínicos e experimentais recentes sugerem que estas alterações teriam relação com o desenvolvimento não só de lesões pré-neoplásicas mas, também, de tumores gástricos. **Objetivo:** Apresentar uma análise qualitativa das alterações anatomopatológicas da mucosa gástrica decorrentes do uso prolongado dos inibidores da bomba de prótons. **Métodos** – Foram utilizados os descritores inibidores da bomba de prótons, lesões pré-neoplásicas e neoplasias gástricas para revisão não sistemática narrativa da literatura, com base nas plataformas Medline, Lillacs e Scielo. Foram selecionados 12 artigos, dentre estudos clínicos (9) e experimentais (3), para análise qualitativa dos resultados apresentados. **Resultados:** A supressão ácida gástrica por altas doses de inibidores de bomba de prótons induz hipergastrinemia e o consequente aparecimento de tumores neuroendócrinos, em modelos animais. As alterações morfológicas encontradas nestes estudos experimentais foram: hiperplasia de células enterochromafins like, tumor neuroendócrino, atrofia, metaplasia e adenocarcinoma.

DESCRITORES - Inibidores da bomba de prótons. Lesões pré-cancerosas. Neoplasias gástricas

Os estudos em humanos, entretanto, apesar de demonstrarem hiperplasia de células enterocromafins like, tumores neuroendócrino e atrofia gástrica, não identificaram metaplasia gástrica ou adenocarcinoma. **Conclusão** Apesar de não ser possível afirmar que o tratamento prolongado com inibidores de bomba de prótons induza ao aparecimento ou acelere o desenvolvimento do câncer gástrico, em humanos, vários autores sugeriram que a administração prolongada poderia promover o desenvolvimento do câncer gástrico. Dessa forma, as evidências demonstradas no modelo animal, bem como o grande número de pacientes que fazem ou que farão tratamento prolongado com esta classe de medicamentos, alertam para necessidade de seu uso mais criterioso, bem como, justificam a manutenção desta importante linha de pesquisa.

INTRODUCTION

For a few decades the long-term use of proton pump inhibitors (PPI) has had wide application in the treatment of several gastrointestinal diseases, such as gastroesophageal reflux, the peptic ulcerous disease, gastritis and non-ulcerative dyspepsia. Recently, however, studies have compared this treatment method with the development of anatomical and pathological changes of gastric mucosa. Probably the most controverted of these changes are glandular atrophy, intestinal metaplasia and neuroendocrine cells hyperplasia. Clinical and experimental studies suggested that these alterations are related to the development of gastric tumors.^{19,21,29}

According to these studies, a probable carcinogenic mechanism involved would be the severe hypergastrinemia, following pharmacological hypochloridia. Gastrin would have trophic effects on enterocromaffin-like (ECL) cells, inducing to hyperplasia and, later, to the development of carcinoid tumors. Another mechanism would be related to an endogenous source of N-Nitrous compounds, potentially carcinogenic, with relevant organotropism to the gastric mucosa. These compounds would be formed from the reduction of nitrates into nitrites, by the production of bacterial nitroreductases. The main bacteria involved would be *Escherichia coli* and *Pseudomonas*, which proliferation would be stimulated by the state of prolonged hypochloridria. Furthermore, these nitrous compounds and their metabolites are inhibited by vitamin C and other antioxidants agents that protect the DNA.^{4,21,23,27,29}

According to Muller *et al.* (2007) the chronic atrophic gastritis, a potential late state of gastric infection by *Helicobacter pylori* (Hp), raises the risk of gastric cancer development up to six times²⁴.

Recently some clinical studies have related the prolonged use of PPI with the progressive worsening of gastritis in patients infected by Hp.^{10,19,26,29}

The aim of this study is to present a qualitative analysis of the anatomopathological changes in the gastric mucosa resulting from the long-term use of PPI, highlighting the important controversy that still exists on this subject.

METHODS

The headings used were proton pump inhibitors, precancerous lesions and gastric tumors for a non-systematic review of the literature, based on the academic search platforms Medline, Lillacs and Scielo. Twelve articles were selected from clinical (9) and experimental (3) studies, for qualitative analysis of the results.

Experimental studies

Souza *et al.* (2002) studied, for 15 weeks, 40 male Wistar rats divided into four groups: G1 (control), G2 (N-Nitroso-N-Methylurea + pantoprazole ®), G3 (pantoprazole ®) and G4 (N-Nitroso-N-Methylurea). Pantoprazole ® was administered 2x/week (14 mg/kg body weight, intraperitoneal injection) and NMU offered ad libitum, diluted in drinking water (100 µg/ml). In the last week were made computer assisted and histological analysis of the gastric mucosa with parietal cells, with main cells and non-oxytic mucosa. They also studied the histological pattern, emphasizing the identification and intensity of atrophy, inflammation, metaplasia and dysplasia.

Hagiwara *et al.* (2010) investigated if there was atrophy worsening in the gastric body in *Mongolian gerbils* rats after a long-term PPI administration. They were divided into four groups of 15 animals each: 1) Hp (ATCC43504); 2) Omeprazole®+Hp; 3) Hp and 4) Control. The *gerbils* had access to food enriched with omeprazole® (100 mg/kg/day) for six months. After that, their stomachs were taken and cut into nine sections (six sections of the fundus and three of the antrum). The gastric mucosa atrophy was evaluated by the lack of parietal cells in the six sections of the gastric fundus. Then, the percentage of the area free from parietal cell was calculated and the degree of the atrophy, studied.

Tsukamoto *et al.* (2011) studied the influence of PPI treatment in the development of tumors based on histological, immunohistochemical and serological analysis of *Mongolian gerbils* infected and non-infected by Hp. A total of 53 animals were divided into six groups: Hp 25PPI, Hp 5PPI, Hp, 25PPI, 5PPI and Control. The group "Hp 25PPI" was infected with Hp and received

the PPI (lansoprazole®) by 25/mg/kg/day. The group "Hp 5PPI", also infected with Hp, received 5 mg/kg/day of lansoprazole®. After 50 and 100 weeks, the animals were sacrificed and samples from the glandular stomach were histological and phenotypically evaluated by use of antibodies against chromogranin A, gastrin and gastric polypeptide inhibitor. The gastrin serum levels were also examined.

Clinical studies

Hage *et al.* (2003) studied, for approximately eight years, twenty-five patients with progressive systemic sclerosis and sixteen with Zollinger Ellison syndrome, who made continuous use of omeprazole® (from 20 to 160 mg). The patients were evaluated from six to twelve months by endoscopy, histopathological analysis of gastric mucosal biopsies and serum gastrin levels.

Rindi *et al.* (2005) studied, for five years, patients in long-term PPI treatment for gastroesophageal reflux disease. Forty-three of them received rabeprazole® 20 mg; forty-four received rabeprazole® 10 mg and thirty-six received omeprazole® 20 mg. During the research period, endoscopic biopsies were done for histopathological studies, highlighting the presence of Hp infection and ECL cells pattern.

Bardhan *et al.* (2005), evaluated the effectiveness and safety of the continued use of pantoprazole® studying patients with peptic ulcer or erosive esophagitis, refractory to H2 blockers or omeprazole treatment; as well as those who underwent aggressive disease (multiple recurrences and complications). After the cure of the previous lesions (ulcers and erosive esophagitis), patients were submitted to maintenance treatment with pantoprazol® (40 mg/day) for five years, at the most. They were observed every three and six months, evaluated by endoscopy and histopathological analysis of body and antrum biopsies, the presence of gastritis, infection by Hp and variations on ECL cells. The gastrin serum levels were also evaluated.

Lundell *et al.* (2006) studied, for seven years, 215 patients with gastroesophageal reflux disease. Ninety-eight were submitted to surgical treatment (gastric fundoplication) and one 117 were treated with omeprazol® (20 to 40 mg). All the patients were evaluated, by endoscopy, on years one, three, five and seven.

Jalving *et al.* (2006), with the purpose of determining if the appearance of glandular polyps was related to the use of PPI, analyzed through esophagogastroduodenoscopy the emergence of glandular polyps in patients who made prolonged use (>1 year) of PPI. Biopsies of the glandular polyps and gastric mucosa were made. There was also an evaluation of the presence of hyperplasia on the parietal cells, their protrusion and the glandular cysts formation.

Hongo e Fujimoto (2010), with the objective of investigating glandular polyp and hyperplastic gastric polyps during the prolonged use of PPI, treated with

rabeprazole 10 mg/day, for approximately two years, patients suffering from reflux esophagitis. They used endoscopy periodically (weeks 1, 24, 52, 76 and 104), and gastric biopsy to evaluate the presence of gastric polyps, mucosa atrophy, infection by Hp and gastrin serum levels.

Fujimoto *et al.* (2011), evaluated the effectiveness and safety use of rabeprazol, for two years, in patients who made daily use of 10 mg for gastroesophageal reflux disease with esophagitis. The patients were evaluated on weeks 1, 24, 52, 76 and 104 through endoscopy, histological studies (presence of atrophies and polyp lesions) and serum dosages of gastrin.

Brunner *et al.* (2012), evaluated tolerance and effectiveness of the continuous use of pantoprazole (40 to 80 mg/day), from four to twelve weeks, studied patients with acute lesions derived from peptic ulcer or gastroesophageal reflux disease. After endoscopy confirmation of the normal mucosa, the patients received daily treatment with pantoprazol® (40 to 160 mg/day) for 15 years. Endoscopy, clinical examination, serum gastrin levels, gastric mucosa histology, and quantification of the endocrine mucosa cells were performed in order to confirm the absence of side effects.

Fiocca *et al.* (2012) studied the endocrine and exocrine gastric mucosa from patients with gastroesophageal reflux disease submitted to anti-reflux surgery, and who received continuous treatment with esomeprazole (20 to 40 mg) for five years. Every two years they underwent endoscopy and biopsies of the pyloric and the gastric body mucosa. There was also evaluation on the levels of gastrin and chromogranin A.

RESULTS

Serum gastrin levels

Bardhan *et al.* (2005) verified that the average gastrin level in Hp infected patients were considerably high. Tsukamoto *et al.* (2011) showed that in Hp infected rats exposed to elevated doses of PPI presented significant increase in the serum gastrin levels. However, the same was not observed on those who received low doses of PPI. Fujimoto *et al.* (2011) observed that the serum gastrin levels increased until the twenty-fourth week, but was stable until the end of the research. Brunner *et al.* (2012) demonstrated a significant augment in the average serum gastrin level in patients who made continuous use of pantoprazol®, although this alteration was not related to significant changes in the gastric mucosa, of clinical relevance.

ECL density/carcinoid tumors

Hage *et al.* (2003) showed that patients without acid hypersecretion and without hypergastrinemia, after a prolonged treatment with omeprazol®, did not present significant ECL proliferation and there

was not the emergence of carcinoid tumors. After the same treatment, however, on patients suffering from Zollinger-Ellison syndrome, the proliferation of ECLs and emergence of carcinoid tumors was verified. There was also observed, in this last group, high serum concentration of gastrin related to chronic gastritis and infection by Hp. Rindi *et al.* (2005) confirmed a strong relationship between hypergastrinemia and the ECL hyperplasia. This research, nonetheless, did not demonstrate the association or evolution of this variation to dysplasia or cancer, after the continued use of omeprazol® or rabeprazol®. It was verified, still, that the main factor related to gastritis was the presence of Hp. However this bacterium did not appear to have strong influence on the extent of the ECL proliferation. Bardhan *et al.* (2005) demonstrated that the total number of endocrine cells in the pylorus had small variation during the research. In the gastric body, however, there was a 1/3 reduction of these cells. The count of gastrin-producing cells showed little alteration in the pylorus, and the numbers tended to be lower in the group infected by Hp. The ECLs and somatostatin-producing cells were present in small quantities, in all cases. Lundell *et al.* (2006) concluded that patients under prolonged use of omeprazol® (20 to 40 mg) showed linear and diffused increase of ECLs, especially on those infected by Hp, on whom they identified strong inflammation of the gastric mucosa followed, in some cases, by glandular atrophy. There were not observed, however, significant metaplastic cell alteration. In the Hp negative patients there was no alteration on the oxyntic exocrine mucosa. Tsukamoto *et al.* (2011), when using lansoprazol® in *Mongolian gerbils* rats observed the appearance of neuroendocrine tumors; but there was no synergy effect between the infection by Hp and the administrations of a high PPI dose. Fujimoto *et al.* (2011) evaluated the gastric mucosa histology in humans and verified the increase of the percentage of G cells and the absence of carcinoid tumors. Brunner *et al.* (2012), studying the density of ECLs, verified an initial increase during the three first years followed by stabilization. There was no increase in the risk of malignancy of these cells observed. Fiocca *et al.* (2012) confirmed a significant augment in the density of ECL cells, after the continued use of esomeprazol®, related to the growth of gastrin and chromogranin A circulation. There was not, however, increase of dysplastic or neoplastic ECL cells.

Chronic gastritis/metaplasia atrophy

Souza *et al.* (2002), studying the effects of a prolonged use of pantoprazol®, demonstrated a significant reduction in the area of the oxyntic gastric mucosa (with both main and parietal cells), and significant growth of the non-oxyntic gastric mucosa area in the stomach of Wistar rats. Bardhan *et al.* (2005) showed that chronic gastritis decreased in the pylorus region and increased in the body, which also

presented atrophic variations. The greatest variations were found in patients infected by Hp. Hagiwara *et al.* (2010) verified significant gastric atrophy in the rats infected by Hp that received omeprazol®. In the same group the presence of adenocarcinoma was more expressive when compared to the group infected only by Hp. Fujimoto *et al.* (2011) demonstrated that there was slight progression of the gastric mucosa atrophy, mainly in patients infected by Hp. Brunner *et al.* (2012), histologically evaluating the gastric body, demonstrated an atrophy increase in Hp positive patients during the first years of treatment, followed by decrease in the end of the research. The Hp negative patients kept, for the whole period, low atrophy degrees. In the pylorus there was constant reduction of the gastric atrophy on patients infected by Hp and initial increase with later decrease of the atrophy on the non-infected patients. There were not found significant metaplastic alterations on both stomach regions. Fiocca *et al.* (2012) verified the prevalence of atrophic lesions and intestinal metaplastic being, however, of small significance in the group of patients submitted to a prolonged use of esomeprazol®.

Inflammatory activity in the gastric mucosa

Brunner *et al.* (2012) found that the lymphocytic infiltration diminished during treatment with pantoprazol®, in the gastric body as well as in the pylorus. However, Hp positive patients showed higher values compared to Hp negative patients. Patients who presented eradication of the Hp during treatment showed significant decrease on the gastritis in the body and pylorus. Fiocca *et al.* (2012) demonstrated that individuals infected by Hp presented a significant reduction of the inflammatory activity of the pylorus mucosa after three years of treatment with esomeprazol®. However, there were not found significant inflammatory alterations in the gastric body of these patients.

Glandular polyps fundic and hyperplastic

Jalving *et al.* (2006) showed that the prolonged use of PPI quadruples the risk of formation of fundic glandular polyps, mainly in patients non infected by Hp. However, the appearance of fundic glandular polyps is not related to dysplastic lesions. It was verified, still, that the continued use of PPIs is related to the hyperplasia and hypertrophy of parietal cells, as well as the formation of glandular cysts. Hongo and Fujimoto (2010) verified that patients infected by Hp presented smaller incidence of fundic glandular polyps when compared to the non-infected. Hyperplastic polyps, however, had a broader occurrence on patients with high gastrin serum levels and on those infected by Hp. Fujimoto *et al.* (2011) observed few fundic and hyperplastic glandular polyp cases on the patients who made daily use of rabeprazol®. Fiocca *et al.* (2012) showed, on individuals non infected by Hp, protrusion

and microcystic expansion in the parietal areas. The same happened to Hp positive individuals, however less expressively.

DISCUSSION

Tsakamoto *et al.* (2010) demonstrated that the suppression of the gastric acid by high doses of PPI induces hypergastrinemia and sequent emergence of neuroendocrine tumors on animals. The massive sustained inhibition of hydrochloric acid together with hypergastrinemia results on important morphological alterations such as ECL cells hyperplasia, which could be one of the initial reasons for the emergence for a neuroendocrine tumor¹.

It is known that the intragastric acidity regulates the gastrin liberation from the G cells of the pylorus, through a negative feedback mechanism, having direct trophic effect on the ECLs. It has been demonstrated that the prolonged acid suppression leads to an increase in the prevalence of hyperplasia on ECL cells, more prominent on individuals infected by Hp when compared to those not infected. Research suggests that the high serum concentration of gastrin related to chronic gastritis and infection by Hp would accelerate the cell proliferation of the ECLs^{3,7,10}.

However, the relationship between stomach carcinoid tumor and hypergastrinemia induced by PPI has not yet been clarified in humans, despite the many clinical studies showing that on those there is also the occurrence of the trophic effect performed by hypergastrinemia, derived from hypochlorhydria, after the continued use of PPI, on ECL cells. There is still controversy about the influence of the infection by Hp on these cells.

The results described by Souza *et al.* (2002) suggest evolution of the atrophy of significant oxyntic gastric mucosa area extent in the stomach of Wistar rats, which were submitted to prolonged use of pantoprazol®. This evolution could pave the way for the development of intestinal metaplasia and, later, for dysplasia or adenocarcinoma areas. According to the author, the absence of these last findings could be related to the limitation in the period of experimental carcinogenesis, as well as to the employed carcinogenic agent dose²⁹.

The serum gastrin levels on animals submitted to high doses of PPI increases approximately 20 times compared to the gastrin levels on animals not submitted to the treatment. In contrast, the long term use of PPI in humans generally results in the increase of two to four times the serum levels of gastrin. Besides that, many studies suggest that human beings have a far lower density of ECL cells than rats. Thus, it is likely that the PPI doses used on clinics are safe and that neuroendocrine tumors would not occur in response to the average dose. Researches show that, on animals submitted to

therapy with low doses of PPI, there is no evidence of the emergence of carcinoma and gastric neuroendocrine tumors, even on animals infected by Hp. This suggests that the use of PPI is clinically safe. However, in high doses, this medicine induces hypergastrinemia and raises the risk of neuroendocrine tumors on animals, showing that a broader understanding towards its use in humans is necessary^{8,12,17,28}.

Recent studies have also demonstrated the relationship between the prolonged PPI use, infection by Hp and gastrointestinal mucosa alterations. The infection by Hp is the primary factor in the progression of gastritis related to the appearance of chronic inflammation, atrophy and intestinal metaplasia, leading to some authors consider such infection like pre malignant condition. Fact can also be found on the research done in 2003 by Rangel *et al.*, who demonstrated that the most relevant risk factor for the occurrence of gastric cancer is the positive urease test. A possible explanation for such a finding would be the growth of gastric pH following acid suppression therapy, which favors the increase of Hp in the area of the gastric body, leading to a more than marked inflammation. Earlier studies have demonstrates, repeatedly, that the short term treatment with PPI induces worsening of the gastritis preexisting in the gastric body of individuals infected by Hp. This could also explain the regression of gastritis in patients whose infection had been eradicated. A study done with patients submitted to the use of omeprazol® and infected by Hp showed pronounced hyperplasia and sharp inflammation. Patients who suffered from the gastroesophageal reflux disease, when not infected by Hp, did not present alterations in the gastric mucosa that would suggest inflammation in consequence of acid suppression induced by PPI. Thus, it is likely that only the suppression would not be capable of having harmful effects on the gastric mucosa. On other researches, where patients under prolonged use of PPI had the Hp eradicated by antibiotic, there was a reduction of the pangastritis and regression of glandular atrophy. Apart from that, the effects of PPIs are more easily detected on patients infected by Hp than on those not infected. Keeping this and the reversibility of the correspondent gastric variations in mind, the suggestion of the eradication of Hp on patients under continued and prolonged PPI based treatment is justified^{2,3,5,6,7,19,25}.

Of potential importance is the observations that some patients under prolonged PPI based therapies develop glandular atrophy of the gastric body. This leads to the preoccupation that the more prolonged the treatment with PPIs, the greater the risk of emergence of atrophic chronic gastritis and, with that, the theoretical risk of gastric tumor development. In experimental studies some authors verified that there is no development of gastric carcinoma in the group of animals submitted to the use of PPI and infected by Hp, nor in the group subject only to high doses of PPI.

However, it is known that the long term use of PPI on *Mongolian gerbils* could generate hypergastrinemia related to atrophic chronic gastritis and ECL cells hyperplasia. Furthermore, researches show that the long term use of this medicine is associated to the increase of the incidence of atrophic chronic gastritis, a precursory condition for stomach cancer^{1,16,31,32}.

Jalving *et al.* (2006) demonstrated that the continued use of PPIs promotes the appearance of fundic hyperplastic polyps, which was also identified by Menegassi *et al.* in 2010. In this last study these findings prevailed on patients over 60 years of age, which could be explained by the longer use of the medicine²².

CONCLUSIONS

Despite the impossibility of affirming that the prolonged treatment with PPIs induces the emergence or accelerates the development of gastric cancer in humans, many authors, using models of experimental gastric carcinogenesis, with animals infected, or not, by Hp, demonstrated or suggested that the prolonged use could provoke the development of gastric cancer, associated to hypergastrinemia, the progression of atrophic gastritis and/or hyperplasia of ECL cells.

The evidence brought by these and other studies, such as the large number of patients that are already, or will be, under continuous use of PPI for many years, justify the maintenance of this important line of research.

The publication of new controlled clinical essays, with the clear indication of the absence of interests in conflict, will certainly contribute to the better enlightenment of the controversy that surrounds this subject.

REFERENCES

- Bardhan KD, Bishop AE, Polak JM, Romanska HM, Rowland A, Thompson M, Morris P, Schaefer-Preuss S, Luehmann R, McCaldin B. Pantoprazole in severe acid-peptic disease: the effectiveness and safety of 5 years' continuous treatment. *Dig Liver Dis* 2005; 37: 10–22.
- Bresciani C, Latif I, Coser RB, Yagi O, Deutsch CR, Mucerino D, Zilberstein D, Cecconelo I. Determinação histopatológica da presença do *Helicobacter pylori* em câncer gástrico. *ABCD Arq Bras Cir Dig* 2011;24(1): 59-63.
- Brunner G, Athmann C, Schneider A. Long-term, open-label trial: safety and efficacy of continuous maintenance treatment with pantoprazole for up to 15 years in severe acid-peptic disease. *Aliment Pharmacol Ther* 2012; 36: 37–47.
- César ACG, Silva AE, Tajara EH. Fatores genéticos e ambientais envolvidos na carcinogênese gástrica. *Arq Gastroenterol* 2002; 39(4):253- 259.
- Coelho LGV, Zaterka S. II Consenso Brasileiro sobre *Helicobacter pylori*. *Arq Gastroenterol* 2005; 42(2):128- 132.
- Filho AD, Santos PB, Duque AS, Cezário RC, Filho PPG. Experimental model in the qualitative and quantitative assessment of non *Helicobacter* gastric microflora under proton pump inhibitors action. *Acta Cir Bras* 2006; 21(5): 279- 284.
- Fiocca R, Mastracci L, Attwood SE, Ell C, Galmiche JP, Hatlebakk J. Gastric exocrine and endocrine cell morphology under prolonged acid inhibition therapy: results of a 5-year follow-up in the LOTUS trial. *Aliment Pharmacol Ther* 2012; 36: 959–71.
- Freston JW. Clinical significance of hypergastrinaemia: relevance to gastrin monitoring during omeprazole therapy. *Digestion*. 1992; 51 Suppl 1:102-14.
- Fujimoto K, Hongo M. Safety and Efficacy of Long-Term Maintenance Therapy with Oral Dose of Rabeprazole 10 mg Once Daily in Japanese Patients with Reflux Esophagitis. *Intern Med* 2011; 50: 179-88.
- Hage E, Hendel L, Gustafsen J, Hendel J. Histopathology of the gastric oxyntic mucosa in two different patient groups during long-term treatment with omeprazole. *Eur J Gastroenterol Hepatol*. 2003; 15:781-89.
- Hagiwara T, Mukaisho K, Nakayama T, Sugihara H, Hattori T. Long-term proton pump inhibitor administration worsens atrophic corpus gastritis and promotes adenocarcinoma development in Mongolian gerbils infected with *Helicobacter pylori*. *Gut*. 2011; 60:624–30.
- Häkanson R, Larsson LI, Liedberg G, Oscarson J, Sundler F, Vang J. Effects of antrectomy or porta-caval shunting on the histamine-storing endocrine-like cells in oxyntic mucosa of rat stomach. A fluorescence histochemical, electron microscopic and chemical study. *J Physiol*. 1976; 259(3):785–800.
- Hassall E, Owen D, Kerr W, Sturby T, Richardson P, El-Serag H. Gastric histology in children treated with proton pump inhibitors long term, with emphasis on enterochromaffin cell-like hyperplasia. *Aliment Pharmacol Ther* 2011; 33: 829–36.
- Hongo M, Fujimoto K. Incidence and risk factor of fundic gland polyp and hyperplastic polyp in long-term proton pump inhibitor therapy: a prospective study in Japan. *J Gastroenterol* 2010; 45: 618–24.
- Jalving M, Koornstra JJ, Wesseling J, Boezen HM, Jong S, Kleibeuker JH. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2006; 24: 1341 –48.
- Kuipers EJ, Lundell L, Klinkenberg-Knol EC, Havu N, Festen HP, Liedman B, Lamers CB, Jansen JB, Dalenback J, Snel P, Nelis GF, Meuwissen SG. Atrophic gastritis and *helicobacter pylori* infection in patients with reflux esophagitis treated with omeprazole or fundoplication. *N Engl J Med* 1996; 334:1018–22.
- Kuipers EJ, Nelis GF, Klinkenberg-Knol EC, Snel P, Goldfain D, Kolkman JJ, Festen HP, Dent J, Zeitoun P, Havu N, Lamm M, Walan A. Cure of *Helicobacter pylori* infection in patients with reflux oesophagitis treated with long-term omeprazole reverses gastritis without exacerbation of reflux disease: results of a randomised controlled trial. *Gut* 2004; 53: 12–20.
- Lamberts R. Morphological changes of the human gastric mucosa under long term proton pump inhibitor therapy and their clinical relevance. *Microsc Res Tech* 2000; 48: 357–66.
- Lundell L, Havu N, Miettinen P, Myrvold HE, Wallin L, Julkunen R, Levander K, Hatlebakk JG, Liedman B, Lamm M, Malm A, Walan A. Changes of gastric mucosal architecture during long-term omeprazole therapy: results of a randomized clinical trial. *Aliment Pharmacol Ther*. 2006; 23:639-47.
- Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakili N, Kuipers EJ. Current concepts in the management of *Helicobacter pylori* infection – the Maastricht III Consensus Report. *Gut*. 2007. 56(6):772-81
- Mccloy RF, Arnold R, Bardhan KD, Cattan D, Klinkenberg- Knol E, Maton PN, Riddell RH, Sipponen P. Pathophysiological effects of long-term acid suppression in man. *Dig Dis Sci*. 1995; 40:116-20.
- Menegassi VS, Czezczko LEA, Czezczko LSG, Ioshii SO, Pisani JC, Junior OR. Prevalência de alterações proliferativas gástricas em pacientes com uso crônico de inibidores de bomba de prótons. *ABCD Arq Bras Cir Dig* 2010;23(3):145-149.
- Mowat ATC, Carswell A, Wirz A, McColl KE. Omeprazole and dietary nitrate independently affect levels of vitamin C and nitrite in gastric juice. *Gastroenterology* 1999; 116:813-22.
- Muller LB, Fagundes RB, Moraes CC, Rampazzo A. Prevalência da infecção por *Helicobacter pylori* das lesões precursoras do câncer gástrico em pacientes dispépticos. *Arq Gastroenterol* 2007; 44(2):93- 98.

25. Rangel MF, Amorim WP, Amorim MFD, Amorim PD, Nóbrega LPS. Avaliação da prevalência da infecção por *Helicobacter pylori* em pacientes com câncer gástrico. *Rev. Col. Bras. Cir.* 2003; 30(1):34-42.
26. Rindi G, Fiocca R, Morocutti A, Jacobs A, Miller N, Thjodleifsson B. Effects of 5 years of treatment with rabeprazole or omeprazole on the gastric mucosa. *Eur J Gastroenterol Hepatol.* 2005; 17:559-66.
27. Rohr I, Ockert D, Reznik GK. Ultrastructural investigations of the enterochromafin-like (ECL) cells in three different rat strains after treatment with the H+K+/ATPase inhibitor pantoprazole. *Exp. Toxic Pathol.* 1992; 44:197-200.
28. Simonsson M, Eriksson S, Håkanson R, Lind T, Lönröth H, Lundell L, O'Connor DT, Sundler F. Endocrine cells in the human oxyntic mucosa. A histochemical study. *Scand J Gastroenterol.* 1988; 23(9):1089-1099.
29. Souza IKF, Silva AL, Misumi A, Savi D, Custódio DS, Maia FFR, Canela GGC, Oliveira CHC. Estudo histológico e computadorizado das áreas com células parietais e principais no estômago de ratos Wistar tratados com pantoprazol e "N-Nitroso-N-Methylurea" (NMU). *Acta Cir Bras.* 2002; 17:251-57.
30. Tsukamoto H, Mizoshita T, Sasaki M, Mizushima T, Tanida S, Ozeki K, Hirata Y, Shimura T, Kataoka H, Kamiya T, Nojiri S, Tsukamoto T, Tatematsu M, Joh T. Long-term High-dose Proton Pump Inhibitor Administration to *Helicobacter pylori*-infected Mongolian gerbils Enhances Neuroendocrine tumor Development in the Glandular Stomach. *Asian Pac J Cancer.* 2011; 12: 1049-54.
31. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. *Helicobacter pylori* infection and the development of gastric cancer. *N Engl J Med.* 2001;345:784-89
32. Ye W, Nyren O. Risk of cancers of the oesophagus and stomach by histology or subsite in patients hospitalised for pernicious anaemia. *Gut.* 2003;52:938-41.