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ORIGINAL ARTICLE

Long-term Acid Suppression Therapy: Its Influence on Gastric Mucosa

Rajesh Prabhu Ponnusamy, Arunkumar Krishnan, Vimala Ramakrishnan, Jayanthi Venkataraman

ABSTRACT

Background/Aim: Long-term acid suppressants are known to have adverse effects. Its effect on gastric mucosa is not known. A cross-sectional study was undertaken to study the effect of *Helicobacter pylori* on gastric mucosa among patients on long-term acid suppressants.

Materials and methods: One hundred and twenty-six patients with symptoms of ulcer type dyspepsia and reflux type dyspepsia for more than a year and on acid suppressants for at least a year were included in the study. Biopsy was obtained from the stomach for demonstration of *H. pylori* and the histological changes. The duration of treatment and presence of *H. pylori* was correlated with the histological changes.

Results: Sixty-six patients were on omeprazole at a dose of 20 mg a day (group I) and the rest were on ranitidine 150 mg twice a day (group II). Demography and the duration of treatment was comparable in both groups. Gastric mucosa was normal in 18 (27.3%) and 30 (60%) patients in groups I and II respectively, which was statistically significant ($p = 0.01$). Intestinal metaplasia was significantly more common among those on proton pump inhibitor (PPI) ($p = 0.05$). None had dysplasia or carcinoma. The colonization of *H. pylori* correlated with the duration of therapy in each of the two groups but was not statistically significant ($p > 0.05$).

Conclusion: Long-term acid suppressants are generally safe. Gastric mucosal changes especially intestinal metaplasia is more common with PPI with fewer mucosal changes when on H_2RA and is not influenced by the presence of *H. pylori*.

Keywords: Proton pump inhibitors, Histamine-2 receptor antagonists, *Helicobacter pylori*, Gastric mucosa.

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INTRODUCTION

Dyspepsia is a common clinical entity, seen often in day-to-day practice.[1] Among them peptic ulcer disease (PUD) is the most common followed by gastroesophageal reflux disease (GERD).[2,3] Acid suppression therapy, both proton pump inhibitors (PPI) and histamine-2 receptor antagonists (H_2RA), are recommended empirical treatment for these patients for symptom relief and often for prolonged periods.[4] The safety of these drugs are well established. Though regarded safe, a few studies have looked into the long-term effects of these drugs on the gastric mucosa.[5-7]

It is a well established fact, that prolonged acid suppression with PPI leads to hypergastrinemia, resulting in gastric mucosal hypertrophy.[8] Carcinoid tumors have been described in rodents after prolonged treatment with PPI, though not described in man.[9,10] Though theoretically, the long-term usage of PPIs are associated with gastric mucosal changes in man, current data do not support a progression from hyperplasia to dysplastic argyrophil cell lesions in the absence of additional genetic factors. On the contrary, H_2RA is a less potent acid suppressant; its safety is also not well established.[11-13] The main factor responsible for progression of chronic gastritis to metaplasia and dysplasia is *Helicobacter pylori*. The bacteria also has an influence on endocrine cell population.[14]

The aim of the present study was to determine the effects of *H. pylori* on gastric mucosa in patients on long-term acid suppression.

Patients and Methods

This was a cross-sectional study conducted at the Department of Gastroenterology, at Stanley Medical College, Chennai, a tertiary referral center in South India. The institution caters to a large population belonging to the lower socioeconomic strata whose average per capita income is approximately Rs 1,000/-. A subspeciality dyspepsia clinic was introduced in 2005, to cater to the needs of patients with dyspepsia symptoms requiring long-term treatment for symptom relief. One hundred and twenty-six patients attending the clinic with symptoms of ulcer type (defined as an epigastric burning sensation or food related pain) or reflux type dyspepsia (heartburn and or regurgitation), for at least a year, age range between 15 and 60 years, belonging to either sex and with a normal upper endoscopy were included for the study. Sixty-six patients were on omeprazole at a dose of 20 mg a day (group I) and the rest were on ranitidine 150 mg twice a day (group II). Based on the duration of therapy, the patients in each group were further subclassified into those taking treatment for less than 2 years, 2 to 5 years and more than 5 years. A detailed demographic profile in each group included age, gender distribution, literacy level, occupational details and per capita income.

Patients in both groups had an upper endoscopy and biopsy from the fundus, body and antrum for rapid urease

test, histology and for demonstration of *H. pylori* using hematoxylin and eosin and modified Giemsa stain. The histological changes in the gastric mucosa were interpreted by the pathologist, who was blinded to the drug details.

The demographic characteristics, details of histopathology were analyzed for statistical significance. Patients with other forms of dyspepsia like dysmotility type or those with combination types were excluded. Those with ulcer type and alarm symptoms, active smokers, recent alcoholics and NSAID abusers and those on antibiotics a fortnight prior to endoscopy were also excluded. Ethics committee of the institution approved the study.

RESULTS

The demography including age, gender distribution, literacy levels, occupation and per capita income were comparable between the two groups ($p > 0.05$) (Table 1). The duration of treatment in the three subgroups was also similar ($p > 0.05$) (Table 2).

Gastric mucosa was normal in 18 (27.3%) and 30 (60%) patients in groups I and II respectively, which was statistically significant ($p = 0.01$). Ten patients (15.2%) in group I and none in group II had intestinal metaplasia ($p = 0.05$) (Table 3). The histological findings when correlated with the duration of treatment did not reveal any significant difference between the two groups except for intestinal metaplasia which showed an increasing trend with prolonged use of proton pump inhibitors (Table 4).

H. pylori colonized predominantly in the fundus in group I and in the antrum in group II. The colonization of *H. pylori* correlated with the duration of therapy in each of the two groups (Table 5). However, these findings were statistically not significant ($p > 0.05$).

When the histological changes were compared between *H. pylori* infected and non-*H. pylori* infected group, it was evident that *H. pylori* was responsible for chronic gastritis and intestinal metaplasia, especially in group I.

Table 2: Duration of therapy in the two groups

Groups	*Group I (%) PPI*	*Group II (%) H_2RA*	*p-value*
Duration (mean month)	38 ± 19.6	42.8 ± 17.1	0.83
6 months to ≤2 years	24 (36.4)	12 (20)	0.35
>2 to ≤5 years	32 (48.5)	36 (60)	
>5 years	10 (15.2)	12 (20)	

Table 3: Histology in patients on PPI and H_2RA

Variables	*Group I (n = 66) (%)*	*Group II (n = 60) (%)*	*p-value*
Normal study	18 (27.3)	36 (60)	0.01
Chronic gastritis	30 (45.5)	14 (23.3)	0.13
Gastric atrophy	12 (18.2)	4 (6.7)	0.33
Intestinal metaplasia	10 (15.2)	0 (0)	0.05
Pit abscess	12 (18.2)	2 (3.3)	0.11

DISCUSSION

The present study has demonstrated histological changes in the gastric mucosa in a cohort of patients on long-term acid suppressants. Studies in the past, in animal models have in rat models carcinoid tumors of enterochromaffin cells, a situation akin to Zollinger-Ellison syndrome. Hypergastrinemia *per se* is known to act as a promoter in hyperplasia-dysplasia and neoplasia sequence.[14]

Based on these observations there is a concern that long-term acid suppressants may predispose to gastric malignancy. In an earlier study, long-term PPI up to 10 years was considered safe. In fact, there has been a general amelioration of antral gastritis and gland atrophy in oxyntic mucosa in patients with reflux disease, without significant changes on atrophy or intestinal metaplasia. However, a worsening of histological changes have been reported in presence of *H. pylori* infection.[15]

Table 1: Demographic characteristics

Variables	*Group I (n = 66) PPI*	*Group II (n = 60) H_2RA*	*p-value*
Age (mean)	39.9 ± 11.4 years	40.6 ± 9.1 years	0.60
M:F	30:36	28:32	0.92
Literacy			
School education	50	42	0.48
College education	2	None	
Illiterate	14	18	
Occupation			
Laborer	40	38	0.82
Professional	None	None	
Unemployed	26	22	
Per capita income			
<500	46	44	0.74
>500	20	16	

Table 4: Correlation of histological changes with duration of therapy

Duration of treatment (Groups I vs II)	*Group I (PPI)*				*Group II (H_2RA)*			
	Normal no. (%)	*Chronic gastritis no. (%)*	*Atrophy no. (%)*	*Intestinal metaplasia no. (%)*	*Normal no.(%)*	*Chronic gastritis no. (%)*	*Atrophy no. (%)*	*Intestinal metaplasia none*
6 months to ≤2 years (24 *vs* 12)	14 (77.8)	6 (20)	2 (16.6)	None	6 (16.7)	4 (28.5)	None	None
> 2 to ≤5 years (32 *vs* 36)	4 (22.2)	18 (60)	6 (50)	3 (42.9)	22 (61.1)	8 (57.1)	4 (100)	None
>5 years (10 *vs* 12)	None	6 (20)	4 (33.3)	4 (57.1)	8 (22.2)	2 (14.2)	None	None

Table 5: Correlation of *H. pylori* prevalence with duration of treatment

Variables	*Group I no. (%)*	*Group II no. (%)*
<2 years	6 (25)	2 (16.7)
2-5 years	10 (41.7)	8 (66.6)
>5 years	8 (33.3)	2 (16.7)

Gudlaugsdotti et al[16] showed that antral inflammation was significantly mild with lower *H. pylori* density and this was independent of Cag A status. However, in Cag A–positive *H. pylori* strain, antral atrophy (p = 0.08) and intestinal metaplasia was common in those on maintenance PPIs when compared to Cag A-negative *H. pylori*-infected patients (p = 0.028). The authors concluded that progression of histological changes in the antrum was determined by Cag A status of *H. pylori* and that PPI accelerated this progression, while reducing the inflammatory infiltrate.

In the present study, gastric mucosal changes were evident with both H_2RA and PPI. With long-term H_2RA, the gastric mucosa was frequently normal or showed mild inflammatory response. *H. pylori* colonization was confined to the antrum with no significant migration. However, in patients on omeprazole the gastric mucosa showed gastric atrophy and intestinal metaplasia. Also *H. pylori* colonization showed a migration from the antrum to the fundus with increasing duration of therapy.

A question arises whether there is a need for an empirical eradication of *H. pylori* prior to recommending long-term acid suppressants especially PPIs to prevent precancerous gastric lesions, such as intestinal metaplasia. Based on our observations, H_2RA as an antisecretory drug appears to be a better option for long-term symptom relief in patients with dyspepsia. Tachyphylaxis, though reported is often not a problem in day to day practice.

Finally, in future, whether long-term use of PPI for dyspepsia is totally safe or not needs to be addressed in larger series, especially in the absence of *H. pylori* infection. The present study has limitations in that this is a cross-sectional study in a group of patients attending the dyspepsia clinic, whose *H. pylori* status at the initiation of the study was not available.

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ABOUT THE AUTHORS

Rajesh Prabhu Ponnusamy

Postgraduate Student, Department of Gastroenterology and Hepatology, Stanley Medical College, Chennai, Tamil Nadu, India

Arunkumar Krishnan (Corresponding Author)

Special Trainee and Research Assistant, Department of Gastroenterology and Hepatology, Stanley Medical College, Chennai, Tamil Nadu India, e-mail: dr.arunkumarpillai@gmail.com

Vimala Ramakrishnan

Professor, Department of Pathology, Coimbatore Medical College Coimbatore, Tamil Nadu, India

Jayanthi Venkataraman

Professor, Department of Gastroenterology and Hepatology, Stanley Medical College, Chennai, Tamil Nadu, India