ANNALS OF GASTROENTEROLOGY 2004, 17(2):133-135

Editorial

Gastric acid inhibitors; impact on gastric and colon cancer

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INTRODUCTION

Drugs inhibiting gastric secretion are the most commonly prescribed daily, in current gastroenterology practice. In addition, other physicians, such as general physicians, internists, reumatologists, cardiologists and orthopaedics quite often prescribe this type of medication. These drugs have been widely engaged in the treatment of peptic ulcer disease and other upper gastrointestinal tract (GI) benign lesions since the late 70's.

The antisecretory drugs include two basic categories; Histamine receptor type 2 antagonists (H2RAs) and Proton Pump Inhibitors (PPIs). These drugs provoke the production of varied gastrin levels, through a positive feed back mechanism, due to a potent gastric acid inhibition. Gastrin has proved to be an important growth factor and a trophic agent, on both gastric and large intestine mucosa, along with stimulation of gastric acid production[1]. Thus, from the very beginning, safety profile concerns were raised with regard to a possible association of long-term antisecretory medication and the development of gastric and colon cancer. In recent years, antisecretory drugs, especially PPI's have frequently been applied in the treatment of patients suffering from gastroesophageal reflux disease (GERD). Many GERD patients need a longer time and higher dosage of antisecretory therapy to control their symptoms. Therefore, the possibility of these drugs provoking de novo appearance or evolution of pre-existing gastric or colon cancer is of profound clinical importance.

The aim of this report is to review the concerns about chronic antisecretory therapy and update the evidence-based data with regard to its safety profile, after many years of clinical experience.

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ANTISECRETORY MEDICATION AND GASTRIC CANCER

To date, at least 6 epidemiological studies (2 cohort and 4 case controls) have reported on the issue of chronic H2RA's therapy (especially cimetidine and ranitidine) and the risk of gastric cancer[3]. According to these studies gastric cancer risk is significantly higher only during the first year of H2RA initiation. The relative risk gastric cancer remains slightly higher over the first five years, but diminishes thereafter. These data do not support a direct correlation between chronic H2RA therapy and the development of gastric cancer. However, the above studies point out that chronic antisecretory therapy may either mask pre-existing neoplasm or delay the diagnosis and appropriate therapy of premalignant lesions of gastric mucosa. Thus, meticulous inspection and biopsies of the gastric mucosa are considered critical prior to treatment contemplation. Unfortunately, there are no epidemiological studies with regard to chronic PPI treatment and gastric cancer risk. However, data coming from many clinical studies, as well as daily clinical experience with PPI (omeprazole or lansoprazole) that were administered over a long period, do not suggest a rise in gastric cancer risk. On the contrary, there are cases of delayed diagnosis of gastric cancer in patients who had received empirical chronic PPI therapy[4].

In theory, long-term PPI treatment could increase the risk of gastric carcinogenesis, by two mechanisms: a) development of chronic hypergastrenaemia and b) reduction of gastric acid secretion and consequent hypochlorhydria[5]. Chronic hypergastrenaemia has been associated with a high risk for the development of gastric cancer. However, recent data failed to support such an association in patients with pernicious anaemia or Zollinger-Ellison syndrome.[6,7] Moreover, patients with ant-

rectomy (low gastrin levels) present a high risk of gastric cancer, while those with vagotomy (high gastrin levels) do not.[8] Therefore, hypergastrenaemia does not seem to be the major risk factor for the development of gastric cancer, though there are some studies showing that patients with gastric cancer have higher gastrin levels compared to controls.[9] Chronic hypochlorhydria due to long-term PPI treatment is another important factor. It has been established that gastric cancer can be developed in patients with hypochlorhydria or achlohydria. However, this may be the result of severe (metaplastic) atrophic gastritis associated with this malignant disease. Hypochlohydria, either due to atrophic gastritis or long-term PPI treatment, blocks the protective effect of the acid on gastric and intestinal mucosa against bacteria. Thus, a consequent bacterial overgrowth ensues, which makes the host more vulnerable to intestinal infections. The rise of bacterial colonisation of gastric mucosa is directly proportional to the degree of reduction of gastric secretion (higher for PPIs, less for H2RAs) and reversible after antisecretory drug discontinuation. Lots of these bacteria present nitroreductase activity and are associated with an increased production of N-nitrosamines that have proved to be carcinogenic in animals. However, recent studies do not report any increase of nitroso-compounds in the gastric juice after omeprazole or cimetidine therapy, despite an increase in bacteria on gastric mucosa[10].

On the other hand, chronic PPI therapy is associated with a deterioration of corpus gastritis in *H. pylori* positive patients[11]. Whether this side-effect could speed up the development of atrophic gastritis is much debated in the literature[12]. Undoubtedly, a deterioration of corpus gastritis provokes further hypochlorhydria and augments the risk of gastric cancer[13]. Moreover, secondary bacteria flora that dominates due to PPI hypochlorhydria could possibly enhance the noxious (and carcinogenic) effect of *H. pylori* on gastric mucosa. Additionally, recent data based on animal models show a synergistic effect of *H. pylori* and hypergastrenaemia on the development of gastric cancer[14]. According to the above, the last consensus in Maastricht (Maastricht 2-2000) recommended *H. pylori* eradication in patients who are going to or already receive long-term PPI treatment, although well designed clinical studies estimating the relative risk of gastric cancer or pre-malignant lesions during long-term PPI treatment are lacking[15].

ANTISECRETORY MEDICATION AND COLON CANCER

Unfortunately, there are no epidemiological studies to estimate the risk of colon cancer in patients receiving PPIs over an extended period. The few existing data have failed to support such a relationship.[3] On the contrary, some antisecretory drugs, like ranitidine and cimetidine, have recently been applied as an adjuvant treatment in operable colon cancer, with favourable results[16]. Animal studies show that hypergastrenaemia, due to long-term omeprazole or ranitidine therapy has no trophic effect on intestinal mucosa and does not promote the development of neoplasia, induced by chemical co-carcinogens[17]. However, there are no similar studies in humans. Moreover, patients with chronic hypergastrenaemia of other cause like pernicious anaemia, Zollinger's-Ellison syndrome or vagotomy have no increased risk of colon cancer compared to controls.[3] There is only one study showing an increased incidence of colorectal cancer among patients with pernicious anaemia during the first five years after diagnosis.[18] This means that chronic hypergastrenaemia may evolute a pre-existing colorectal neoplasia. The existing studies on the incidence of indigenous hypergastrenaemia in patients with adenomatous colorectal polyps or cancer present conflicting results[5,9]. However, recent studies have shown that patients with indigenous hypergastrenaemia have a 3-4 fold risk of colorectal polyps or cancer compared to controls[19,20]. Additionally, significant genetic expression of gastrin and the specific gastrin receptor (gastrin/CCKB) has been found, even in the very early events of the development of adenomatous colorectal polyps. This makes polyps exceptionally susceptible to the high gastrin levels of systemic circulation and promotes the adenoma-carcinoma sequence[21].

These data cannot establish a direct association between long-term antisecretory therapy and colorectal cancer. However, a current hypothesis could be that, in genetically predisposed people, chronic hypergastrenaemia due to antisecretory drugs could accelerate the early events in the development of colorectal premalignant lesions (polyps) and their evolution to carcinoma. The accuracy or otherwise of the above hypothesis can only be tested with well-designed, long-term, prospective studies.

CONCLUSIONS

In summary, long-term antisecretory drug treatment is generally safe and not associated with a high risk of gastric or colorectal cancer. However, people at high risk for premalignant gastric lesions or gastric cancer should undergo gastroscopy, prior to initiation of long-term antisecretory drug therapy (especially with PPIs). It is also recommended that long-term PPIs users receive *H. pylori* eradication therapy, although there are no conclusive clinical studies supporting this recommendation, so far. To date, there is insufficient data supporting a significant effect of chronic hypergastrenaemia due to PPIs on the evolution of colorectal polyps to carcinoma. Thus, there is no reason to change the existing guidelines for screening, surveillence and management of these lesions in patients who receive antisecretory medication long-term.

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