# Neoplasia due to PPIs. A comment to Editorial in “Gastroenterology” .

Subjects: Allergy

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The gastric hormone gastrin is released when the gastric content acidity is too low to efficiently kill swallowed microorganisms. Gastrin stimulates the ECL cell to produce histamine which in turn stimulates the acid producing parietal cell to secrete acid. Parallel to the stimulation of the ECL cell function, gastrin also stimulates the ECL cell proliferation. Prolonged elevation of gastrin results in ECL cell hyperplasia and further to ECL cell neoplasia of varying malignancy known from about 1980. The proton pump inhibitors (PPIs) are the most efficient inhibitors of acid secretion and are very efficient in the treatment of acid related diseases or symptoms. Before their acceptance for clinical us, PPIs were known to induce neoplasia in rodents, but the medical community accepted that these tumors were not relevant for man. With time there have been accumulating evidence for PPI induced neoplasia also in man. However, very recently a large observation study financed by a pharmaceutical company, patients were followed for an average of 3 years without any evidence of neoplasia. The study was published in "Gastroenterology" and resulted in an "Editorial" claiming that the truth was approached. Unfortunately, the "Editorial " did not consider animal studies and recent studies in man reporting increased risk of gastric cancer in patients on PPI after eradication of Helicobacter pylori compared with those not taking PPI after eradication. Therefore the "Editorial" was flawed and I wrote a letter commenting on these errors. After 2 weeks I got a refusal claiming that my letter was without relevance and importance. I found that peculiar, and I also mean that a journal has an obligation to print letters showing faults with papers published and especially concerning a misleading "Editorial". I therefore publish my letter allowing others to evaluate the relevance and importance

Gastric cancer gastrin proton pump inhibitors

**Rejected letter to “Gastroenterology"**

I read with interest and astonishment the editorial by Corley [1] based upon a multinational observational study of pantoprazole treatment compared with placebo followed for about 3 years by Moayyedi et al. [2]. They did not find evidence of any harmful effect on the kidneys or the cardiovascular system where previous epidemiological studies have suggested increased risk of disease. This was to be expected since there were no plausible mechanisms for these side effects. However, based upon the Moayyedi study Corley also seems to conclude that there is no reason to worry about neoplasia due to long-term PPI therapy. As I see it, this reflects lack of biological, physiological and pathological knowledge, because:

1: Cancer is mainly a disease of old age reflecting years of development. Three years say nothing. Children in a Spanish family with a missense mutation in one of the proton pump genes developed ECL carcinoids in their twenties and more malignant tumor in the thirties [3, 4] which is in line with the latency in animal studies done in the

1980s [5, 6]. This Spanish family is the best model for long-term PPI treatment in man and underscores that one should be particularly reluctant to put children on PPI treatment. The tumors both in the animals and the Spanish family[6] [3-5] were due to hypergastrinemia secondary to hypoacidity. Moreover, Håkanson et al.[7] found that long-term PPI dosing of rats induced a positive trophic effect only in the oxyntic mucosa and particularly the ECL cell. It is therefore strange that the focus during all the years with PPIs has not been on gastric cancer [8]. Since 1990 we have published multiple studies describing ECL cell/neuroendocrine differentiation in human gastric carcinomas [8, 9]. I have wondered why pharmaceutical industry has not supported a study disapproving the role of the ECL cell in gastric carcinogenesis[10] and thus taken away an important argument for a risk of hypergastrinemia and PPI treatment. Such a study would have been much more important with respect to cancer than the Moayyedi study. In fact, to assess cancer risk we must rely on studies on animals with a much shorter life span than man. Accordingly, Moayyedi study is without value with respect to cancer.

It is also very peculiar that Helicobacter pylori (Hp) in combination with PPI treatment is not mentioned, since it is confirmed in studies from East Asia that PPI treatment after Hp eradication increases the risk of gastric cancer [11-13]. Hp gastritis is the principal cause of gastric cancer [14], and Uemura et al. showed that Hp gastritis predisposes to gastric cancer only after having induced atrophy of the oxyntic mucosa [15]. Since not only Hp oxyntic atrophic gastritis, but also autoimmune atrophic gastritis predisposes to gastric cancer [16], we have argued that Hp gastritis causes gastric cancer via hypergastrinemia [17]. Anyhow, the studies from East-Asia [11-13] cannot be dismissed.

2: Biological function of gastric juice.

The biological function of the highly acid gastric juice is to kill swallowed microorganism. In the study by Moayyedi [2] this aspect is only sparsely covered, but it seems that there was an increased risk of enteric infections[2]. We do not know the etiology of most of the chronic inflammatory diseases as well as degenerative disease of the central nervous system, but infectious agents could be the cause of many of these diseases. The gut is a possible entrance for infections by micro-organisms escaping destruction in the stomach as exemplified by poliomyelitis. Variant Creutzfeldt-Jacob disease in man due to intake of meat contaminated with pathogenic prion is another example of such a disease. In this context I will mention that we have described that mice given scrapie infected brain were more prone to develop disease when dosed with PPI [18]. It should be recalled that many infections may cause disease after decades of latency.

To conclude, for complications with a latency of decades the study by Moayyedi et al.[2]is of little value, and we must rely on biological knowledge and animal studies. The editorial by Corley lacks completely these aspects [1]. I prefer to rely more on the evolution than imperfect studies.

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