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Editorial

Does proton pump inhibitor therapy promote gastric polypoid lesion formation?

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Proton pump inhibitors (PPI's) have been widely used for the treatment and prophylaxis of acid–related diseases. These drugs are therefore prescribed extensively, often for minor complaints.[1,2] In the last decade there have been reports of PPI's being associated with gland–type gastric polyps.[3,4]

Fundic gland–type polyps are common benign polyps of the gastric body and fundus, generally small, and composed of dilated glands lined by normal cell types of the oxyntic mucosa, with a mixture of parietal cells, chief cells, and mucus neck cells. Many fundic gland polyps are sporadic and single, but cases with multiple fundic gland polyps have been reported as fundic gland polyposis (FGP) in patients without FAP, or in similar terms.[5] The relationship between sporadic fundic gland polyps (SFGP) and FAP – associated polyps-remains unclear, and SFGP remain poorly characterized at the clinical, histological, and molecular level. It is not clear whether SFGP forms a distinct entity from patients with a single or few polyps or whether there is a continuum between these two groups. According to Torbenson et al,[6] sporadic polyps are linked to activating b–catenin mutations, whereas FAP–associated with fundic gland polyps, are caused by second somαtic hits in the adenamatous polyposis coli gene.

A possible correlation between fundic gland polyps and use of PPIs was first reported in a study by Graham et al in 1992[7] and has also been noted in a number of subsequent studies. Choudhry et al,[8] reported an interesting case in which polyps appeared after introduction of PPI therapy, disappeared after withdrawal of these drugs and appeared again after the reintroduction of PPI's. Although low-grade dysplasia has been reported in a small percentage of fundic gland polyps, there has been no report of progression to high–grade dysplasia or carcinoma. These stand in contrast to fundic gland polyps in the setting of FAP, where dysplasia and adenocarcinoma have been noted in a significant percentage of polyps.[9,10]

It is well known that gastric acitidy kills swallowed microorganisms, and acid secretion must be of biological importance, because it is maintained in phylogenesis. Acid secretion is controlled by feedback mechanisms, mainly via gastrin. A decrease in acitidy always causes an increase in plasma gastrin. The trophic effect of gastrin leads to hyperplasia and neoplasia of the enterochromatin–like (ECL) cell. ECL cell derived tumours in man were previously regarded as rare, and also as rather benign. It is now clear that the ECL cell gives rise to a significant proportion of gastric carcinomas. Moreover, ECL carinoids secondary to hypergastrinaemia may develop into highly malignant tumours.[1] Although inhibitors of gastric acid secretion, mainly PPIs, have been reported to cause minor side effects, it should be recalled that omeprazole (the first proton pump inhibitor) was temporally stopped due to enterochromatin-like cell carcinoids in the oxyntic mucosa of rats, secondary to hypergastrinaemia following life–long treatment with omeprazole. Thus, the drung induced tumours in the targets organs. Not only PPI's, but also others inhibitors of gatric acid secretion, like H_2–blockers tend to induce ECL cell carcinoids in rats and may be related to a degree of acid inhibition and not to any specific group of drugs. The use of PPIs produces more profound acid inhibition and, thus, more severe hypergastrinemia than H_2–stillblockers. In contrast to proton pump inhibitors, there is a tendency to tolerance development with the long–term use

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of H^2–blockers, which reduces the efficacy of these drugs and thus their hypergastrinaemic effect.[1,2]

Despite the suspected link between PPIs and some cases of fundic gland polyps, there is little information available on possible mechanisms. One possibility is that PPI's may cause b-catenin mutations although this may be not detectable in the early histological change of PPIs therapy. A second possibility is that PPIs secondarily lead to fundic gland polyps. Gastrin is known to be a growth factor for the oxyntic mucosa. PPIs are also known to cause modest elevations in serum gastrin levels, but, in several studies SFGP has not been associated with elevated serum gastrin levels.[1]

In conclusion, sporadic fundic gland polyps are typically seen in middle-aged patients of both genders with histories of PPIs therapy. Most polyps were small and showed the typical histology of single fundic gland polyps. Because the long–term significance of these polyps is uncertain, prospectives studies of their natural history are required. According to recent literature, the possibility that gastrin can induce long-term side effects related to profound acid inhibition of gastric acid secretion, due to long-term use of PPIs cannot be ruled out. It is therefore reasonable to be cautious with the long-term use of potent inhibitors of gastric acid secretion, especially in young individuals.

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