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Mini Review

Proton Pump Inhibitors - An Overview

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Production of acid in the upper gastrointestinal tract was developed in primitive fishes and has been preserved during evolution. Together with enzymes, the proteolytic enzyme pepsin, and a lipase, both being active at the extreme acidic condition in the stomach, the gastric juice is a liquid extremely suited for killing swallowed microorganisms. Although protein digestion starts in the stomach, the main function of the gastric juice is to kill micro-organisms and thus protect the organism from infections via the gut. The production of gastric acid is one of the most energy requiring processes in the body by creating a H+ gradient of more than 1 million. This is also reflected by the parietal cells being stuffed with mitochondria. The susceptibility of the oxyntic mucosa to hypoperfusion/hypoxia is also reflected by stress ulcers developing in the oxyntic mucosa [1]. Moreover, the evolutionary importance of the highly acidic gastric juice is indirectly demonstrated by the risk it creates by causing breaks in the mucosa leading to peptic ulcer or reflux oesophagitis. The gastric and duodenal bulb mucosae protect themselves by secreting bicarbonate into a surface mucin layer, but sometimes the acid and enzymes overwhelm the defence leading to mucosal breaks. The squamous epithelium in the oesophagus lacks these abilities but is protected by a valve function due to the anatomy as well as muscular tone. When the valve function by one cause of the other is defect, gastric juice enters the oesophagus causing damage to the mucosa, reflux oesophagitis.

For many years the focus was on the harmful effects of the gastric juice, and then mainly the gastric acid. In this context it should be mentioned that the effects of the gastric juice are due to a combination of the acid and the active enzymes, and that it is impossible to separate the one from the other. The biological function of the gastric juice has been neglected, probably due to the apparent few problems in patients lacking gastric acidity as those having autoimmune gastritis and anacidity. Due to the prevalent problems due to gastric acidity, there were early great interest in the production and regulation of gastric acid. Thus, Pavlov initiated physiological studies on living animals describing the importance of nerves in the regulation of gastric acid secretion [2], and Edkins postulated the production and release of an antral hormone, gastrin, stimulating acid secretion [3]. Some years later Popielski described the acid stimulatory effect of histamine [4]. Thus, the three major gastric acid secretagogues were known, but their interaction was heavily disputed during at least seventy years. By physiological studies using strips of oxyntic mucosa in Ussing chambers Rangachari made findings indicating that gastrin worked via histamine [5], and Swedish authors studying gastric acid secretion in isolated oxyntic glands and isolated parietal cells indirectly by consumption of oxygen or accumulation of the weak base aminopyrine, could not find any effect of gastrin in contrast to the two other secretagogues [6]. With the completely isolated rat stomach model we showed that maximal gastrin-stimulated acid secretion was inferior to that of maximal histamine-stimulated [7] and that gastrin released histamine [8] in quantities sufficient to explain its acid stimulatory effect [9].

The cell producing and releasing the histamine taking part in the regulation of acid secretion was disputed for many years. The mast cell was believed to be the actual cell although it had no fixed localization with respect to the parietal cells or oxyntic glands. In the late sixties Håkanson et al. described the ECL cell as a histamine producing cell in the rat [10], but the ECL cell was not accepted as the cell producing the histamine taking part in the stimulation of acid secretion in man and other species before the middle of the eighties [11]. The ECL cell reaches the parietal cell by elongations resembling neurons [12], and the ECL cell and not the parietal cell expresses the gastrin receptor [13].

Before the recognition of Helicobacter pylori as the main cause of peptic ulcer, compounds inhibiting gastric acid secretion were sought to treat patients with peptic ulcer. Anticholinergic drugs had some effect, but due to side effects did not become popular. The first drug with sufficient efficacy and specificity in inhibiting gastric acid secretion and thus treatment of peptic ulcer was the histamine-2 blocker cimetidine [14]. New histamine-2 blockers with increased potency were developed and commonly used until the introduction of the first proton pump inhibitor (PPI), omeprazole in the late eighties. PPIs bind covalently to the proton pump, the final step in acid secretion, and thus blocks acid secretion independently of the way of stimulation [15]. The PPIs had an unprecedent ability to reduce acid secretion and heal lesions due to gastric acidity, and therefore became very popular and soon replaced older less efficient drugs. Since peptic ulcer disease can be cured by Helicobacter pylori eradication, reflux oesophagitis became the main indication for PPI use. However, not only those with oesophagitis, but also patients with acid regurgitation without oesophagitis experienced symptomatic

relief with the use of PPIs, and PPI use thus become prevalent. For some reason or the other, gastro-oesophageal reflux disease seems to have increased in prevalence during the last decades. Moreover, patients with functional dyspepsia are claimed to have a symptomatic effect by PPI treatment [16], further increasing the number of subjects using PPI [17].

PPIs have few side effects directly related to the compound itself. The problems with PPIs use are related to their biological function; profound acid inhibition resulting in reduced gastric acidity leading to loss of the ability to kill swallowed micro-organisms and the secondary hypergastrinemia in an in vain response to restore gastric acidity. Only in the recent years there have been some concern related to the loss of the biological activity of the gastric juice leading to change in enteral microbiome [18], although we had described increased susceptibility for prion disease in mice dosed with inhibitors of gastric acid secretion many years ago [19,20]. The role of the gut as entrance for micro-organisms has probably been underestimated which is of concern taking into consideration the lack of knowledge of the cause of chronic and degenerative diseases as well as cancers [21]. Nevertheless, in this short review I will concentrate on the problems/danger with hypergastrinemia.

Gastrin not only stimulates function of the ECL cell (synthesis and release of histamine), but has also a specific trophic effect on this cell [22] resulting in hyperplasia [23]. The ECL cell hyperplasia causes increased gastrin-stimulated histamine release [24] which will increase gastrin-stimulated acid secretion leading to rebound acid hypersecretion [25]. In normal subjects PPI dosing for some weeks resulted in dyspeptic symptoms from one week after stopping PPI dosing [26] showing that the ECL hyperplasia lasted longer than the acid inhibitory effect of PPI. The problem in termination with PPI treatment when first started may be due to such a mechanism [27].

The consequence of the trophic effect of gastrin due to PPI induced hypoacidity was realized at an early phase in the development of the first PPI, omeprazole, by the occurrence of ECL cell derived tumours in the oxyntic mucosa of rats dosed long-term with omeprazole [28]. Later ECL cell derived tumours induced by hypergastrinemia have been described in different rodent species [29-31]. Also in man, but naturally after a longer period of hypergastrinemia, ECL cell derived tumours of type neuroendocrine tumours (NETs), have been described [32-34]. Furthermore, gastric carcinoma related to PPI use has been described [35], and in a case-control study patients continuing with PPI after Helicobacter pylori eradication resulted in gastric cancer more often than in those not using PPI [36], and in a population based cohort study significantly more gastric cancers occurred in a group of PPI users compared with histamine-2 blocker users [37]. Also, meta-analysis has shown increased occurrence of gastric cancer in PPI users [38]. There are many other papers showing or indicating increased prevalence of gastric cancers in PPI users. Thus, it can be no doubt that PPIs predispose to gastric cancer. The magnitude of the increased cancer risk due to PPI is presently thought to be low and in a recent paper it was concluded that the administration of PPIs to patients with functional dyspepsia was worth the risk of developing gastric cancer [39]. It has, however, to be remembered that carcinogenesis often can be a slow process as reflected in gastric cancer which usually is a disease of old age. There is therefore every reason to fear that more cases of gastric cancer due to PPI will occur.

The role of the ECL cell in gastric carcinogenesis has hitherto been underestimated. We found ECL cell/neuroendocrine differentiation in gastric carcinoma cells many years ago [40-42] and also showed expression of the gastrin receptor on these cancer cells [43]. Moreover, the PAS positive material in cancer cells in signet ring cell carcinomas, believed to be mucin, was negative for mucin both by immunohistochemistry and in-situ hybridization [44]. Therefore, we have argued for a reclassification of gastric carcinomas of diffuse type according to Lauren [45] from adenocarcinomas to neuroendocrine carcinomas [46].

The interaction between PPI use and Helicobacter pylori infection is important. Thus, it was rather early recognized that PPI use in patients with Helicobacter pylori gastritis could increase the inflammation [47]. Moreover, in spite of tremendous work during thirty years, no Helicobacter pylori factor responsible for the carcinogenic effect has been found. It was thus very important when it was shown that Helicobacter pylori gastritis predisposed to gastric cancer only after having induced oxyntic atrophy [48]. On this background we have for years claimed that the carcinogenesis by Helicobacter pylori was due to hypergastrinemia secondary to reduced gastric acidity [49,50]. This mechanism also explains why patients having had eradication of Helicobacter pylori or having lost the infection due to anacidity may develop gastric cancer many years afterwards [51]. The practical consequences of these facts are that patients starting with long-term PPI treatment should be tested for Helicobacter pylori and have eradication if possible. Furthermore, patients having had Helicobacter pylori infection are probably more at risk of gastric cancer due to PPI [36]. In the future, when a specific and efficient gastrin antagonist like netazepide [52,53] becomes commercially available, cancer may probably be prevented by such agents when used in those at highest risk.

In conclusion, PPI use may induce gastric cancers occurring in the oxyntic mucosa being of the relatively benign NET type, but also neuroendocrine carcinomas. Since carcinogenesis takes long time, there is every reason to fear that the prevalence of these cancers will increase. The biological consequences of taking away the function of gastric juice with respect to infections via the gut remains to be seen.

REFERENCES

1. HL Waldum, R Mårvik, JE Grønbech, AK Sandvik, S Aase. Oxyntic lesions may be provoked in the rat both by the process of acid secretion and also by gastric acidity. Aliment Pharmacol Ther. 2000; 14: 135-141.
2. Pavlov I. The Work of the Digestive Glands. 1902.
3. Edkins JS. The chemical mechanism of gastric secretion. J Physiol. 1906; 34: 133-144.
4. Popielski I. β-Imidazolylyathyamin und die Organextracte Ester. Teil. 1920; 178: 214-236.
5. Rangachari PK. Histamine release by gastric stimulants. Nature. 1975; 253: 53-55.

6. T Berglindh, HF Helander, KJ Obrink. Effects of secretagogues on oxygen consumption, aminopyrine accumulation and morphology in isolated gastric glands. Acta Physiol Scand. 1976; 97: 401-414.

7. PM Kleveland, HL Waldum, H Larsson. Gastric acid secretion in the totally isolated, vascularly perfused rat stomach. A selective muscarinic-1 agent does, whereas gastrin does not, augment maximal histamine-stimulated acid secretion. Scand J Gastroenterol. 1987; 22: 705-713.

8. AK Sandvik, HL Waldum, PM Kleveland, B Schulze Søgnen. Gastrin produces an immediate and dose-dependent histamine release preceding acid secretion in the totally isolated, vascularly perfused rat stomach. Scand J Gastroenterol. 1987; 22: 803-808.

9. Waldum HSA. Gastric functional and trophic receptors for CCK. In Aspects of synaptic transmission:acethylcholine, sigma receptors, CCK and eicosaniods, neurotoxins. Edn. Taylor and Francis Ltd. 1993; 157-172.

10. Hakanson R, Lilja B, Owman C. Cellular localization of histamine and monoamines in the gastric mucosa of man. Histochemie. Histochemistry. Histochimie. 1969; 18: 74-86.

11. R Håkanson, G Böttcher, E Ekblad, P Panula, M Simonsson, M Dohlsten, et al. Histamine in endocrine cells in the stomach. A survey of several species using a panel of histamine antibodies. Histochemistry. 1986; 86: 5-17.

12. Björn I Gustafsson, Ingunn Bakke, Øyvind Hauso, Mark Kidd, Irvin M Modlin, Reidar Fossmark, et al. Parietal cell activation by arborization of ECL cell cytoplasmic projections is likely the mechanism for histamine induced secretion of hydrochloric acid. Scand J Gastroenterol. 2011; 46: 531-7.

13. I Bakke, G Qvigstad, AK Sandvik, HL Waldum. The CCK-2 receptor is located on the ECL cell, but not on the parietal cell. Scand J Gastroenterol. 2001; 36: 1128-1133.

14. JW Black, WA Duncan, CJ Durant, CR Ganellin, EM Parsons. Definition and antagonism of histamine H 2 -receptors. Nature. 1972; 236: 385-390.

15. Sachs G, Wallmark B. Biological basis of omeprazole therapy. J Gastroenterol Hepatol. 1989; 4: 7-18.

16. Christopher J Black, Lesley A Houghton, Alexander C Ford. Insights into the evaluation and management of dyspepsia: recent developments and new guidelines. Therap Adv Gastroenterol. 2018; 11: 1756284818805597.

17. Anton Pottegård, Anne Broe, Jesper Hallas, Ove B Schaffalitzky de Muckadell, Annmarie T Lassen, Anders B Lødrup. Use of proton-pump inhibitors among adults: a Danish nationwide drug utilization study. Therap Adv Gastroenterol. 2016; 9: 671-678.

18. Mariko Hojo, Takashi Asahara, Akihito Nagahara, Tsutomu Takeda, Kohei Matsumoto, Hiroya Ueyama, et al. Gut Microbiota Composition Before and After Use of Proton Pump Inhibitors. Dig Dis Sci. 2018; 63: 2940-2949.

19. TC Martinsen, D M Taylor, R Johnsen, HL Waldum. Gastric acidity protects mice against prion infection? Scand J Gastroenterol. 2002; 37: 497-500.

20. Tom C Martinsen, Sylvie L Benestad, Torfinn Moldal, Helge L Waldum. Inhibitors of gastric acid secretion increase the risk of prion infection in mice. Scand J Gastroenterol. 2011; 46: 1418-1422.

21. Waldum H, Martinsen TC. Chronic diseases: what about infections of virus and prions via the gut? Therap Adv Gastroenterol. 2021; 14: 17562848211028805.

22. I Bakke, G Qvigstad, E Brenna, AK Sandvik, HL Waldum. Gastrin has a specific proliferative effect on the rat enterochromaffin-like cell, but not on the parietal cell: a study by elutriation centrifugation. Acta Physiol Scand. 2000; 169: 29-37.

23. R Lamberts, W Creutzfeldt, F Stöckmann, U Jacubaschke, S Maas, G Brunner. Long-term omeprazole treatment in man: effects on gastric endocrine cell populations. Digestion. 1988; 39: 126-135.

24. HL Waldum, T Lehy, E Brenna, AK Sandvik, H Petersen, BS Søgnen. Effect of the histamine-1 antagonist astemizole alone or with omeprazole on rat gastric mucosa. Scand J Gastroenterol. 1991; 26: 23-35.

25. HL Waldum, JS Arnestad, E Brenna, I Eide, U Syversen, AK Sandvik. Marked increase in gastric acid secretory capacity after omeprazole treatment. Gut. 1996; 39: 649-653.

26. Christina Reimer, Bo Søndergaard, Linda Hilsted, Peter Bytzer. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. Gastroenterology. 2009; 137: 80-87.

27. E Björnsson, H Abrahamsson, M Simrén, N Mattsson, C Jensen, P Agerforz, et al. Discontinuation of proton pump inhibitors in patients on long-term therapy: a double-blind, placebo-controlled trial. Aliment Pharmacol Ther. 2006; 24: 945-954.

28. Havu N. Enterochromaffin-like cell carcinoids of gastric mucosa in rats after life-long inhibition of gastric secretion. Digestion. 1986; 35: 42-55.

29. D Poynter, SA Selway, SA Papworth, SR Riches. Changes in the gastric mucosa of the mouse associated with long lasting unsurmountable histamine H2 blockade. Gut. 1986; 27: 1338-1346.

30. G Cui, G Qvigstad, S Falkmer, AK Sandvik, S Kawase, HL Waldum. Spontaneous ECLomas in cotton rats (Sigmodon hispidus): tumours occurring in hypoacidic/hypergastrinaemic animals with normal parietal cells. Carcinogenesis. 2000; 21: 23-27.

31. O Nilsson, B Wängberg, L Johansson, IM Modlin, H Ahlman. Praomys (Mastomys) natalensis: a model for gastric carcinoid formation. Yale J Biol Med. 1992; 65: 741-751.

32. CS Jianu, R Fossmark, T Viset, G Qvigstad, O Sørdal, R Mårvik, HL Waldum. Gastric carcinoids after long-term use of a proton pump inhibitor. Aliment Pharmacol Ther. 2012; 36: 644-649.

33. Edith Lahner, Emanuela Pilozzi, Gianluca Esposito, Gloria Galli, Bruno Annibale. Gastric carcinoid in the absence of atrophic body gastritis and with low Ki67 index: a clinical challenge. Scand J Gastroenterol. 2014; 49: 506-510.

34. McCarthy DM. Proton Pump Inhibitor Use, Hypergastrinemia, and Gastric Carcinoids-What Is the Relationship? Int J Mol Sci. 2020; 21: 662.

35. Constantin S Jianu, Ove J Lange, Trond Viset, Gunnar Qvigstad, Tom C Martinsen, Reidun Fougner, et al. Gastric neuroendocrine carcinoma after long-term use of proton pump inhibitor. Scand J Gastroenterol. 2012; 47: 64-67.

36. Ka Shing Cheung, Esther W Chan, Angel Y S Wong, Lijia Chen, Ian C K Wong, Wai Keung Leung. Long-term proton pump inhibitors and risk of gastric cancer development after treatment for Helicobacter pylori: a population-based study. Gut. 2018; 67: 28-35.

37. Devin Abrahami, Emily Gibson McDonald, Mireille E Schnitzer, Alan N Barkun, Samy Suissa, Laurent Azoulay. Proton pump inhibitors and risk of gastric cancer: population-based cohort study. Gut. 2022; 71: 16-24.

38. Daniel Segna, Nele Brusselaers, Damian Glaus, Niklas Krupka, Benjamin Misselwitz. Association between proton-pump inhibitors and the risk of gastric cancer: a systematic review with meta-analysis. Therap Adv Gastroenterol. 2021; 14: 17562848211051463.

39. Efrat Broide, Adi Eindor-Abarbanel, Haim Shirin, Vered Richter, Shay Matalon, Moshe Leshno. Is administration of proton pump inhibitors in functional dyspepsia worth the risk of developing gastric cancer: a Markov model to bridge the gap between scientific evidence and clinical practice. BMJ Open. 2020; 10: e031091.

40. HL Waldum, OA Haugen, C Isaksen, R Mecsei, AK Sandvik. Enterochromaffin-like tumour cells in the diffuse but not the intestinal type of gastric carcinomas. Scand J Gastroenterol Suppl. 1991; 180: 245-249.

41. HL Waldum, S Aase, I Kvetnoi, E Brenna, AK Sandvik, U Syversen, et al. Neuroendocrine differentiation in human gastric carcinoma. Cancer. 1998; 83: 435-444.

42. Tom C Martinsen, Nan E T Skogaker, Reidar Fossmark, Ivar S Nordrum, Arne K Sandvik, Marianne Ø Bendheim. Neuroendocrine cells in diffuse gastric carcinomas: an ultrastructural study with immunogold labeling of chromogranin A. Appl Immunohistochem Mol Morphol. 2010; 18: 62-68.

43. Patricia Mjønes, Ivar S Nordrum, Øystein Sørdal, Liv Sagatun, Reidar Fossmark, Arne Sandvik. Expression of the Cholecystokinin-B Receptor in Neoplastic Gastric Cells. Horm Cancer. 2018; 9: 40-54.

44. Øystein Sørdal, Gunnar Qvigstad, Ivar Skjåk Nordrum, Arne K Sandvik, Bjørn I Gustafsson, Helge Waldum. The PAS positive material in gastric cancer cells of signet ring type is not mucin. Exp Mol Pathol. 2014; 96: 274-278.

45. Lauren P. The two histological main types of gastric carcinoma: Diffuse and so-called intestinal-type carcinoma. An attemt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965; 64: 31-49.

46. Helge Waldum, Patricia Mjønes. Time to Classify Tumours of the Stomach and the Kidneys According to Cell of Origin. Int J Mol Sci. 2021; 22: 13386.

47. EJ Kuipers, L Lundell, EC Klinkenberg-Knol, N Havu, HP Festen, B Liedman, et al. Atrophic gastritis and Helicobacter pylori infection in patients with reflux esophagitis treated with omeprazole or fundoplication. N Engl J Med. 1996; 334: 1018-1022.

48. N Uemura, S Okamoto, S Yamamoto, N Matsumura, S Yamaguchi, M Yamakido, et al. Helicobacter pylori infection and the development of gastric cancer. N Engl J Med. 2001; 345: 784-789.

49. HL Waldum, A Sandvik, E Brenna. Gastrin, the enterochromaffinlike cell, and gastric tumors. Gastroenterology. 1993; 105: 1264-1266.

50. Helge L. Waldum, Liv Sagatun, Patricia Mjønes. Gastrin and Gastric Cancer. Front Endocrinol (Lausanne). 2017; 8: 1.

51. Susumu Take, Motowo Mizuno, Kuniharu Ishiki, Chiaki Kusumoto, Takayuki Imada, Fumihiro Hamada, et al. Risk of gastric cancer in the second decade of follow-up after Helicobacter pylori eradication. J Gastroenterol. 2020; 55: 281-288.

52. Malcolm Boyce, Andrew R Moore, Liv Sagatun, Bryony N Parsons, Andrea Varro, Fiona Campbell, et al. Netazepide, a gastrin/cholecystokinin-2 receptor antagonist, can eradicate gastric neuroendocrine tumours in patients with autoimmune chronic atrophic gastritis. Br J Clin Pharmacol. 2017; 83: 466-475.

53. R Fossmark, Ø Sørdal, C S Jianu, G Qvigstad, I S Nordrum, M Boyce, et al. Treatment of gastric carcinoids type 1 with the gastrin receptor antagonist netazepide (YF476) results in regression of tumours and normalisation of serum chromogranin A. Aliment Pharmacol Ther . 2012; 36: 1067-75.

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