Proton pump inhibitors and gastric cancer: a long expected side effect finally reported also in man

We read with interest the report by Cheung *et al* describing increased risk of gastric cancer in patients treated long-term proton pump inhibitor (PPI) after *Helicobacter pylori* eradication.[1] On the same day, a Swedish study also reported increased risk of gastric cancer in patients having been treated long-term with PPI.[2] Since cancers in general most often require decades to develop, the magnitude of the PPI-related cancer risk cannot be foreseen. For 30 years, we have worked with the role of gastrin and the risk of PPI treatment with respect to gastric cancer and published more than 200 papers and letters in this field. However, our publications have for one reason or the other been overseen and not discussed. On the other hand, since we always have concluded that PPI treatment in the long term would cause gastric cancer, it is strange that producers of PPIs have not done studies to dismiss our results. However, the gastric cancer risk linked to PPI treatment should have been anticipated as early as in the late 1980s.

Around 1980, it became clear that hypergastrinemia, either due to gastrinoma in MEN1 patients with increased gastric acid secretion or secondary to atrophic gastritis with gastric hypoacidity, resulted in ECL cell neuroendocrine tumours. Bordi asked whether they were hormonally induced. The interest for such tumours increased dramatically when PPIs as well as the insurmountable histamine-2 blocker loxtidine caused ECL cell tumours in the rat.[3] Glaxo then stopped developing loxtidine, whereas Astra continued with omeprazole in clinical trials. At meetings arranged by the PPI manufacturer, with most experts within gastric pathology and gastroenterology present, it was concluded that the ECL cell did not play any appreciable role in human gastric carcinogenesis. Omeprazole was accepted for use in patients with severe diseases due to gastric acid hypersecretion. However, PPIs were soon used in less severe cases and are now prescribed to patients with minor complaints from the upper abdomen (10% of the population in the Western world).

We recall Kenneth Wormsley's words about the acceptance of omeprazole for clinical use: "The first compound accepted for use in humans after having induced cancer in its target organ"; a taboo was broken. Moreover, the claim that the ECL cell was insignificant in gastric carcinogenesis was flawed. ECL derived gastric carcinomas had been described already in the late 1970s. It was also evident that the distinction between adenocarcinomas and neuroendocrine carcinomas was difficult in both humans[4] and rodents. In rodents, we demonstrated that the gastrin receptor was localised to the ECL cell and not to the parietal cell[5] and that gastrin stimulated ECL cell histamine release and proliferation at rather low concentrations. We then turned to pathology, and by using the most specific and sensitive methods available to study ECL cell markers in gastric carcinomas, we found such differentiation particularly in carcinomas classified as diffuse according to Lauren,[6–8] notably in almost all carcinomas from patients with pernicious anaemia displayed ECL cell markers.

Early, it was recognised that PPIs induced hypergastrinemia and ECL cell hyperplasia.[9] In a proportion of patients, gastrin was found to be elevated, but most often, only slightly. It must be recalled that blood gastrin measured 24 hours after the last PPI intake is a trough value and that the 24 hours integral is far more important with regard to ECL cell proliferation. Like in the rat, where the tumorigenesis starts with hyperplasia and then develops into neoplasia of increasing malignancy, the same initial event was found in man. It therefore seems naïve to believe that the process halts in man, whereas it continues only in the rat. All processes take less time in short-lived animals compared with man.

Recently, a study from Finland found that patients with high gastrin values in samples from the eighties had increased risk of gastric cancer,[10] and we have proposed

that even the carcinogenic effect of *H. pylori* infection is best explained by the hypergastrinemia secondary to oxyntic atrophy.

We conclude that the carcinogenic effect by PPI treatment is due to hypergastrinemia, which should have been realised decades ago before exposing so many patients to a risk of a serious disease.

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