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Leading article

Inhibition of acid and gastric carcinoids

Control of gastric acid secretion has long been one of the principal aims of medical and surgical approach to the management of peptic ulcer disease. Prolonged maintenance treatment with more and more powerful drugs now appears to be on the horizon.

Extensive testing of loxtidine, a very potent histamine H_2 antagonist which differs from cimetidine and ranitidine in that it offers non-competitive and insurmountable H_2 antagonism[1] is reported by Dr Poynter and his colleagues in this issue.[2] These data and other studies, raise a number of interesting questions about the biology and pathophysiology of the gastric endocrine cells. Poynter *et al*, using stringent necropsy protocols have found a striking incidence of neuroendocrine gastric carcinoid tumours of a non-functional variety when loxtidine was administered in high doses to male and female Wistar rats for the whole of their natural life span. The first tumour appeared 712 days after starting the drug and female rats appear to be more susceptible than males. The progressive histological changes ranging from intramucosal proliferation of neuroendocrine cells to the formation of small tumours and subsequent invasion through the muscularis mucosa, were taken to indicate early malignancy. Full malignant potential was evinced in one rat only by replacement of a lymph node by malignant cells. These findings are interesting, as spontaneous tumours of the glandular stomach in the rat are very rare and spontaneous carcinoids are not recorded. The authors' hypothesis appears straightforward enough: profound inhibition of gastric acid secretion, which presumably occurred at the doses of loxtidine used, abolished luminal acid inhibition of antral G cells and lead to secondary hypergastrinaemia which in turn could stimulate enterochromaffin-like cells,[3] producing hyperplasia and eventual neoplasia. There was no evidence of a dose response relationship, however, indicating perhaps that all doses of loxtidine used were well into the supramaximal range for complete acid inhibition. The authors do not report serum or plasma gastrin concentrations in this study.

Support for their hypothesis comes from the well documented changes seen in idiopathic fundic mucosal atrophy in man where diffuse endocrine cell hyperplasia mainly of enterochromaffin-like cells has been reported.[4–7] Similarly hypergastrinaemia in association with fundic atrophic gastritis has also been associated with nodules of endocrine cells termed microcarcinoids.[8–10] Nevertheless, in general, gastric carcinoids are rare, constituting only 3% of all gastrointestinal carcinoids[11–13] and approximately 0·3% of all gastric tumours.[12] A recent review of 123 patients with pernicious anaemia, screened by endoscopy, disclosed four patients with a solitary, and one patient with multiple gastric carcinoid tumours.[14] In these cases serum gastrin concentrations ranged from 1060 to 7500 pmol/l. The tumour

cells stained positively in immunohistochemical analysis using antibodies for neurone specific enolase (a reliable marker for tissue of neuroendocrine origin), and this is similar to the observations of Dr Poynter and his colleagues in the rats given loxtidine. Fundic mucosal endocrine cell hyperplasia and hypergastrinaemia were also noted by Carney *et al*,[15] but whether the proposed series of events leading to endocrine cell hyperplasia and neoplasia is directly associated with hypergastrinaemia is not proven. It is interesting that gastric carcinoid tumours have also been detected in the Zollinger-Ellison syndrome[15 16] where serum gastrin concentrations are sometimes higher than in pernicious anaemia. As gastrin is known to stimulate enterochromaffin-like cells[17] it is probably that the common factor in the development of gastric carcinoids is hypergastrinaemia and not profound inhibition of gastric acid secretion, as was present in the toxicological study in rats reported by Poynter *et al.* In some clinical cases of gastric carcinoid, gastric adenocarcinoma has been found concomitantly.[11 13 15–21] No suggestion of gastric adenocarcinoma was present in the loxtidine study and this was in contrast to the response in the rat to the histamine H_2 antagonists tiotidine[22] and SKF93479,[23] which after 12 months of high dosage produced adenocarcinomas of the stomach on the one hand and hyperplasia and hyperkeratosis of the forestomach on the other. Extensive toxicological studies with conventional H_2 blockers in the rat did not produce any gastric tumours. Loxtidine itself when tested by the WHO nitrosation procedure yielded no mutagenic products. Moreover, the development of gastric carcinoid tumours is entirely different from that seen after treatment with a nitrosated derivative of an H_2-receptor antagonist, which produced adenocarcinoma in an experimentally wounded rat's stomach.[24]

It is interesting that in experiments with very high doses of ranitidine (2000 mg/kg/day) lasting from 875 to 903 days with plasma gastrin concentrations as high as 8900 mg/ml Poynter *et al*, did not find any evidence of enterochromaffin-like cell hyperplasia or carcinoid tumours.[25] Was this because ranitidine is a competitive H_2 blocker, while loxtidine has a non-competitive action? This observation suggests that factors other than hypergastrinaemia may be involved. In a recent 24 month carcinogenicity study using omeprazole,[26] a proton pump blocker, six of 60 male and 24 of 60 female rats receiving omeprazole 400 μmol/kg/day developed gastric carcinoids. The strikingly higher incidence in the female than in the male rats was particularly marked at the lower doses of the drug used in the study (40 and 125 μmol/kg/day). A study in mice with omeprazole did not yield focal argyrophilic cell hyperplasia, or carcinoid tumours. These results with a different compound tested in the same species are very similar to the loxtidine study reported in this issue of *Gut*. The evidence to date suggests that the effects on enterochromaffin-like cells in such models are not dependent on the molecular structure of the drug producing profound inhibition of gastric acid, but are probably associated with the severity and duration of hypergastrinaemia. As it is well known that there is no close correlation between luminal gastric hydrogen ion activity and serum gastrin, it is likely that in man serum gastrin concentration is influenced by other factors, such as vagal stimulation, hypercalcaemia and the presence of antral gastritis as well as by intragastric pH.[27–29] An interesting and as yet unexplained finding in the loxtidine and omeprazole

experiments and on long term treatment in the rat with a new H_2 receptor blocker famotidine,[30] was the occurrence of eosinophilic granules in cells adjacent to the chief cells in the basal parts of the gastric glands.

A preliminary report has highlighted the importance of the gastric antrum in rats treated with omeprazole (10–400 μmol/kg orally), or ranitidine (175+175; μmol/kg orally), compared with antrectomised rats given omeprazole (400 μmol/kg orally).[31] Gastrin concentrations increased in rats with intact stomachs treated with the drugs but they were low in antrectomised controls: detailed studies showed a direct significant correlation between concentrations of plasma gastrin and enterochromaffin-like cell density, and with tissue levels of histidine decarboxylase and histamine. These results support the hypothesis that prolonged inhibition of gastric acid secretion and the resulting hypergastrinaemia causes proliferation of the enterochromaffin-like cells.[3] There was no evidence of any direct effect of either omeprazole, or ranitidine on enterochromaffin-like cell density and the same is probably true of the studies with loxtidine. All of these studies were done in the rat with very high doses of the drugs.

Who needs such profound and prolonged acid inhibitions? From many points of view it is not desirable in man. This is because of the putative dangers of gastric colonisation and nitrosamine formation,[32–36] in addition to the risk of gastric carcinoid tumours. Extrapolation of data from rat to the human is difficult as in some ways the rat is less sensitive to the action of some gastrointestinal hormones, for example gastrin, than is man. The production of epithelial and endocrine cancers, however, in association with profound inhibition of gastric acid secretion experimentally recalls Emerson's words: 'Nothing in nature is given, everything is sold'. As in other fields, there is a strong suggestion that nature has done the experiment herself many times in the past,[11–15] and it may be that the luminal pH of the stomach has little if anything to do with gastric carcinoids, providing that the hypergastrinaemia reaches as yet an undefined threshold. The ability of antrectomy to prevent these changes in the body and fundus of the stomach is also of fundamental importance in understanding the mechanism of pharmacologically induced gastric carcinoids, but the question remains why so relatively few clinical cases have occurred in those with profound and prolonged hypergastrinaemia, as in pernicious anaemia and in the Zollinger-Ellison syndrome. These observations highlight the dangers of extremes and emphasise the need to avoid prolonged excessive suppression, or excessive stimulation of the gastric cells. Are there other modulating factors? In a few patients with gastric carcinoids assays of some 20 peptides including somatostatin have been normal and 24 hour urinary 5-HIAA secretion was also normal in the five patients tested.[14] It may be that with treatment for longer and longer periods with increasingly powerful H_2 blockers or with omeprazole, which has recently been shown to be very effective for the Zollinger-Ellison syndrome,[37] the need for endoscopic surveillance, multiple biopsies and argyrophil staining of specimens from these special cases will become much more important.

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