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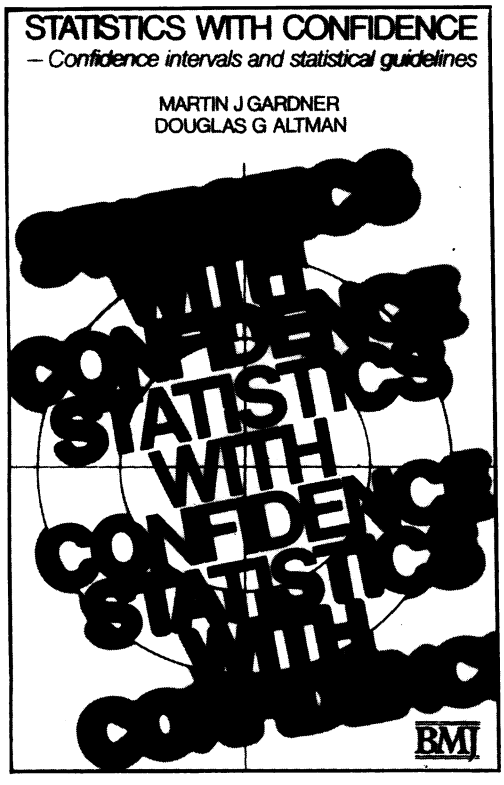

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pharmacological agents of high potency and long duration of action, which when given to animals in large doses for their natural life spans may produce changes difficult to interpret in terms of potential risk for man. Such is the case with powerful inhibitors of gastric acid secretion where the finding of ECL cell hyperplasia and gastric carcinoids in rodents has caused concern. Any logical attempt at the extrapolation of these findings to the clinical situation must involve an exercise in which relevant similarities and differences between animal and man are weighed.

Studies designed to display carcinogenic hazard are usually conducted in mice and rats treated for their natural life spans with high daily doses. Unlike man spontaneous tumours of the glandular stomach are rare in rodents which, as they are experimentally susceptible, must mean that they do not normally come into contact with significant quantities of environmental gastric carcinogens. Simply expressed it is evident that rodents kept under controlled laboratory conditions do not get stomach cancer whereas man in his uncontrolled environment does. Acid suppression in the rodent produced by H_2 blockade or proton pump inhibition has been particularly studied in the rat where hypergastrinaemia is followed by hyperplasia of the fundic neuroendocrine ECL cells.[1] Potent antisecretory agents such as omeprazole and loxtidine have further been associated with malignant changes of such cells in the form of gastric carcinoid tumours.[2-4] Whereas the hyperplastic response is predictable and occurs in many animals, however, in only some were malignant carcinoids seen. Because the studies were designed to last for the natural life span of the rodents and as hypergastrinaemia and ECL cell hyperplasia occur shortly after the commencement of treatment it is surprising that if, as proposed, hyperplasia slips inexorably into microcarcinoidosis and carcinoid formation then more do not show malignancy. There must surely have been enough time for such changes to develop. Other factors may be involved. It is possible that over the relatively long periods of time involved the achlorhydric state has encouraged the formation of carcinogens which act on the already hyperplastic ECL cells to render them neoplastic. In this event it would not be too surprising if in the rat the first indication of a malignant change consequent upon marked acid suppression was the development of a carcinoid and not an adenocarcinoma.

Further evidence that the achlorhydric environment might present a risk was seen in mice given loxtidine,[4] an unsurmountable H_2 receptor antagonist, where in addition to the marked atypical hyperplasia and carcinoid formation in the gastric fundus there also appeared signs of early incomplete metaplasia; a change which is, in man, regarded as a precancerous condition. Are all the pathological changes seen in the stomachs of mice and rats attributable to hypergastrinaemia?

A simple extrapolation from gastric carcinoid tumours in rodents to similar tumours in man cannot be done without an understanding of the nature of gastric tumours, especially important are the differences and similarities between carcinoids and carcinomas, both of which are malignant tumours of gastric epithelial cells. If the tumour is of glandular origin it is a carcinoma; if it is of neuroendocrine origin it is a carcinoid. As it is now accepted, however, that the stomach stem cell is pluripotent it is perfectly acceptable to refer to a gastric carcinoid as a gastric neuroendocrine carcinoma and some authors do this. Further as the stem cell is pluripotent it is not surprising that many human gastric adenocarcinomas contain neuroendocrine cells and that composite tumours composed of adenocarcinoma and carcinoid are recognised. Although clinically different carcinoma and carcinoid may be regarded as poles of a spectrum of gastric neoplasia. This was well illustrated in a rat given loxtidine where the obvious malignant carcinoid in the mucosa took on a decided glandular form as it infiltrated below the muscularis mucosa.

It is necessary before consideration is given to the clinical use of omeprazole or other compounds producing considerable periods of achlorhydria to ask what other changes may be present in the gastric mucosa of patients having peptic ulcer disease. As we age, atrophic gastritis becomes common and in this condition the epithelial cells fail to repress DNA synthesis and undergo abnormal maturation as they migrate through the gastric mucosa. Further, atrophic gastritis is accompanied by pseudopyloric metaplasia of body glands or by metaplasia towards an intestinal type of epithelium with its associated histological and histochemical features. In fact intestinal metaplasia occurs only in epithelium which is already the seat of chronic gastritis or gastric atrophy.[5] When it is appreciated that intestinal metaplasia has been recognised as a precancerous condition since 1955[6] it is pertinent to ask if it is likely to be present in ulcer disease. As it is known that duodenal ulcer, hyperacidity and antral gastritis are commonly associated[7] and also that in gastric ulcer atrophic gastritis is present in both fundus and antrum,[8] it is apparent that the gastric mucosae of such patients may already be in a precancerous condition, in that metaplastic changes will be present. Of special concern is incomplete metaplasia because various studies strongly suggest a close relationship to gastric carcinoma.[8] It may well be injudicious to produce profound and long lasting suppression of gastric acid particularly in patients whose stomachs already show precancerous conditions.

Direct comparison of omeprazole 20 mg om and ranitidine 150 mg bid shows marked differences in median hourly intragastric acidity in duodenal ulcer patients observed for 24 hours after a total of 28 days of treatment. With ranitidine acidity reached 60 mmol/l whereas with omeprazole values were usually nil rising no higher than 10 mmol/l on one occasion.[9] In a separate study[10] it was found that ranitidine treatment given in the same way was associated with significant positive correlations among pH, nitrate concentration and bacterial counts but that despite these changes, an acid tide at some point in each 24 hours prevented persistent bacterial colonisation of the stomach. Even after nine to 12 months of maintenance ranitidine (150 mg nocte) there was no significant effect on the concentrations of nitrite or N-nitroso compounds. The analysis of the N-nitroso compounds was performed by C L Walters who also participated in a further study[11] in which 30 mg of omeprazole per day was given for two weeks. As expected omeprazole had a considerably more potent antisecretory effect than ranitidine. The highest acidity recorded reached just over 20 mmol/l. Twenty two hours after the last dose of omeprazole there were significant increases in the bacterial count and also, in contrast with ranitidine, significant increases in the nitrite and N-nitrosoamine concentrations. As the N-nitroso group is associated with carcinogenicity the effect of sustained treatment with omeprazole must cause concern.

The rodent studies performed with new antisecretory compounds must be considered in relationship to man. Malignant changes, if found, must be evaluated, simple extrapolation to man considering only carcinoid tumours is not enough. Powerful compounds such as omeprazole and loxtidine may produce enough acid suppression to allow bacterial overgrowth and the formation of N-nitroso compounds. Such compounds are known to be associated with carcinoma and their effect on precancerous gastric changes may well be of significance.

I believe that physicians should only use powerful antisecretory agents which produce persistent effects on parietal cells, for conditions unresponsive to established therapy.

D POYNTER
Hoddeson
Herts

Dr Poynter was formerly the Director of Pathology at Glaxo Group Research; he is now retired but is retained by that company as a consultant.

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NOTES

European Digestive Disease Week

This meeting of the European Association for Gastroenterology and Endoscopy will be held in Vienna, Austria from 5–9 June, 1990. Further information may be obtained from Univ Doz Dr H Pristautz, Medizinische Universitätsklinik Graz, Auenbruggerplatz 15, 8036 Graz, Austria.