*Occasional report***Assessing the safety of drugs for the long-term treatment of peptic ulcers**

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Two clinical features of ulcer disease (and related, or associated, diseases such as oesophagitis) are of cardinal importance in determining the nature of anti-ulcer therapy – the tendency of the disease to relapse and the likelihood that repeated relapses will occur for many years: perhaps throughout the lifetime of many patients.¹ At some time during the life of patients with an ulcer, relapse results in haemorrhage in one-third of affected individuals² and in perforation in about 10%³ so that any relapse is potentially lethal. The aim of the treatment of ulcer disease must therefore be to prevent relapse.

At present there is no drug therapy which 'cures' ulcer disease – that is, there is no treatment which is not followed by relapse of the ulcers when treatment is discontinued. On the other hand, it has been repeatedly shown recently that continuous treatment with the H₂ receptor antagonist cimetidine⁴ or ranitidine^{5, 6} can maintain ulcers in remission while other, albeit shorter, studies indicate that continuous treatment with pirenzepine^{7, 8} and sucralfate^{9, 10} can also keep ulcers healed. Even continuous administration of the presently available anti-ulcer drugs for more than five years, however, does not seem to have altered the underlying tendency of ulcers to relapse when treatment is stopped. It seems, therefore that long-term continuous treatment with drugs prevents ulcer relapse only if given for many years and perhaps for life.

Implications of long-term therapy

Drugs which are going to be used continuously for many years must undergo rigorous testing for toxicity in life-long animal experiments. In addition

to general toxicity, however, other problems can be predicted from the specific pharmacological actions of anti-ulcer drugs and these must also be properly evaluated. The most important of these effects is the inhibition of gastric secretion by action on the gastric parietal cells, an effect which is achieved by blockade of specific receptors, such as the histamine H₂ receptor (cimetidine, ranitidine), or gastric muscarinic receptor (pirenzepine), or by inhibiting intracellular messengers (polycyclic drugs such as trimipramine, mianserin, quisultidine), or by interfering with the specific processes involved in the secretion of acid (substituted benzimidazoles, such as omeprazole, which inhibit the K⁺.H⁺-ATPase of the parietal cells).

The gastric secretory inhibitors may give rise not only to drug-specific disorders, but also possibly have adverse effects in common, as a result of pharmacological inhibition of gastric secretion. In this context the most serious hypothetical problem is the possibility that prolonged gastric secretory inhibition may result in the development of gastric cancer.^{11, 12} Although no confirmation has been provided by rigorous surveillance during treatment,¹³ the matter has aroused widespread public concern.

Proposed mechanisms of gastric carcinogenesis

Several mechanisms have been proposed by which gastric inhibitory drugs can, theoretically, cause gastric cancer:

(1) The drug or its metabolite may turn out to be a genotoxic (initiating) carcinogen.^{14, 15} For example, while cimetidine and ranitidine are neither mutagenic nor genotoxic, both drugs can be nitrosated *in vitro*¹⁶⁻²⁰ with the production of genotoxic derivatives. These *in vitro* findings are unlikely to be of any clinical importance, because the strongly acid conditions and excess of nitrous

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acid which are essential for the nitrosation of ranitidine are not encountered in the stomach^{17 19} and the gastric juice of patients treated with ranitidine is devoid of mutagenic activity.¹⁹ Similarly, nitrosocimetidine has not been detected in the gastric juice of patients during treatment with the drug.²¹ Neither cimetidine²² nor ranitidine¹⁷ has produced gastric cancer in experimental animals and neither of the nitrosated drugs is carcinogenic.^{21 23 24}

Thus the extensive experimental and clinical information available from long term use of cimetidine and ranitidine does not support the hypothesis that gastric secretory inhibitors cause gastric cancer

In contrast, it has been reported that the H₂ receptor antagonist tiotidine, which like cimetidine has a nitrosatable side chain, produces carcinomas of the gastric antral mucosa of rats,²⁵ similar to those produced by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), a confirmed gastric carcinogen in rats.²⁶ In addition, another H₂ receptor antagonist – SK&F 93479 – has produced reversible focal hyperplasia and hyperkeratosis of the mucosa of the forestomach of rats treated with the drug for one year.²⁷ Longer studies with SK&F 93479 have been done, but information about the outcome of these studies is not yet available. Similar reversible pre-neoplastic lesions, however, occur in the rat forestomach during treatment with methylnitrosourea²⁸ and develop into frank squamous cell carcinoma if the treatment is continued.

Although the mechanism by which these two drugs have produced proliferative and neoplastic gastric lesions have not been defined, the similarity with the effect of two nitroso-compounds suggests that the drugs, or their derivatives, may also have acted directly as genotoxic carcinogens. Unfortunately, available information does not permit definitive inference^{29 30} about the genotoxic potential of these drugs.

(2) Alternatively, it has been suggested that therapeutic gastric inhibition produces conditions which may promote^{14 15} the development of gastric cancer^{21 31 32} as the incidence of gastric cancer is unexpectedly high in patients with impaired gastric secretion, in conditions such as pernicious anaemia;^{33–35} chronic atrophic gastritis^{35–37} and after gastric resection.^{35 38 39} The hypothesis states that the decreased secretion of acid permits colonisation of the stomach by bacteria, some of which are capable of reducing salivary and dietary nitrate to nitrite.^{40 41} Subsequently, the nitrite reacts with constituents (secondary or tertiary amines, or amides, peptides, etc) of normal gastric juices⁴² and

with food proteins⁴³ to form nitroso compounds which are carcinogenic.

It has often been overlooked, however, that the hypothesised nitrosation involves the formation of nitrous acid and nitrous anhydride from nitrite, reactions which require the presence of hydrogen ions – that is, gastric acid,⁴⁴ so that conditions associated with achlorhydria are unsatisfactory for the formation of nitroso compounds. On the other hand, nitrogen oxides react experimentally with aliphatic and heterocyclic amines in neutral or alkaline aqueous conditions, while acidic pH is inhibitory.⁴⁵ This aspect of the formation of nitroso compounds appears not to have been satisfactorily studied in the context of intragastric contents and its role in the production of nitroso compounds in the gastric lumen during anti-ulcer therapy cannot be assessed at present.

It is, therefore, not surprising that some published studies seem to confirm each step of this hypothesis of achlorhydria-associated gastric carcinogenesis, but other studies provide contradictory information,^{46–49} so that factual evidence for the hypothesis remains uncertain. In any case, much more study is needed to confirm the allegedly increased production of possibly carcinogenic nitroso compounds in the stomach during treatment with gastric secretory inhibitors. It has been reported in a few studies that the concentration of nitroso compounds is increased in the gastric contents of individuals treated with gastric anti-secretory drugs.^{50 32 41} So, of course, is the concentration of everything, because the secretion of diluting gastric juice is inhibited. There is no evidence that the production of nitroso compounds is increased. Indeed, in patients with atrophic gastritis in whom the production of nitroso compounds was studied by the administration of nitrate and proline, urinary excretion of nitroso-proline was not increased and the urinary levels were highest in subjects with an intragastric pH of about 2.⁵¹ It is important that the problem should be studied properly in patients treated with anti-secretory drugs, rather than verbally extrapolated as at present. This is because increased production of nitroso compounds (if it occurs) may be expected to magnify the risk not only to the stomach, but perhaps even more to the gall bladder, the urinary bladder, or the colon: it is in these organs that any absorbed and excreted nitroso compounds will be concentrated and remain in contact with the mucosa even longer than in the stomach.

(3) In any case, it must be emphasised that the proposed connection between decreased, or absent gastric secretion and gastric cancer is not established either experimentally, or clinically. Indeed, in the

three human precancerous diseases of the gastric mucosa (pernicious anaemia, chronic atrophic gastritis and the postgastrectomy mucosa) the attention paid to the proposed pathogenic role of decreased gastric secretion in the development of gastric cancer has probably been misplaced. After all, the decreased gastric secretion is merely a manifestation of the severe disease of the gastric mucosa, which has resulted in substantial or total loss of the acid secreting parietal cells.

It is in this context that another explanation for the increased tendency of the diseased gastric mucosa to undergo malignant change must be considered. In all three types of diseased gastric mucosa marked abnormalities of cellular proliferation and differentiation are present.^{36 52-54} It has been shown previously that proliferating tissues in general are susceptible to genotoxic carcinogens⁵⁵ and epigenetic (promoting) carcinogens act, at least in part, by causing cellular proliferation^{15 56} which sensitises to (and even may activate) the effects of an initiating carcinogen by inducing abnormal proliferation of (initiated) cells with defective auto-regulatory control processes.¹⁴ It seems (to me) probable that the noxious effect of drugs on the state of proliferation and differentiation of the gastric mucosa is going to be the most important criterion of carcinogenic risk, unless the drugs are confirmed genotoxic carcinogens. That being the case, the presently available H₂ histamine receptor antagonists (cimetidine, ranitidine) are without risk, as it seems that these two drugs do not affect the cellular kinetics of the gastric mucosa,⁵⁷ nor produce the changes of gastritis.^{58 59} The mucosal condition during therapeutic gastric secretory inhibition by these two drugs seems to be quite normal and normally resistant to carcinogens, while at the same time fundamentally different from the circumstances of the gastric mucosa in the gastric preneoplastic diseases.

The possibility, however, that some other gastric secretory inhibitors may act as promoters by stimulating the proliferation of the gastric mucosa has been highlighted by the recently reported results of long-term studies of two new drugs of this type. Life span oral administration (>2 years) of loxidine (an unsurmountable H₂ histamine receptor antagonist) to rats and mice produced marked hyperplasia and malignancy of the gastric glandular mucosa of a type not described previously (personal communication). Even more recently it has been reported that administration of omeprazole for two years produced increased numbers of carcinoid tumours of the rat gastric mucosa. Mice and dogs were not affected (personal communication).

Clearly, both loxidine and omeprazole produce

gastric proliferation predisposing to, or actually causing, gastric neoplasia in the rat – but unless there are remarkable strain differences, the trophic stimulus from these two powerful gastric inhibitors must be different. No information is available about the mechanism of the trophic effect of loxidine. Omeprazole produces hypergastrinaemia in man⁶⁰ and it has been proposed that prolonged administration of omeprazole to rats results in continuous and long term hypergastrinaemia, which in turn produces the carcinoid tumours. It was previously reported that antral exclusion in rats stimulated the growth of the endocrine cells of the rat stomach^{61 62} and it had been argued that the associated hypergastrinaemia was responsible for the trophic stimulant effect on the gastric endocrine cells. In human atrophic gastritis there is also often proliferation of gastric mucosal endocrine cells⁶³ and carcinoid tumours have been described in the stomach of patients with pernicious anaemia.^{64 65} Both of these gastric mucosal diseases are accompanied by hypergastrinaemia. While the proposed connection between hypergastrinaemia and the proliferation and neoplasia of the gastric endocrine cells is therefore possible, other trophic factors may also be involved. Thus it has been reported that antrocolic transposition in the rat is not accompanied by significant hypergastrinaemia, and yet there is marked growth of the duodenal mucosa in these animals,⁶⁶ presumably triggered by another trophic factor. It has been suggested that in man, as in animals, the drug-induced achlorhydria results in hypergastrinaemia because the normal inhibition of gastrin release from the antral G cells is lacking, because acid (which inhibits gastrin release) is absent from the antral lumen. This point has not been confirmed experimentally. Moreover, gastrin has not been reported to stimulate the proliferation of G cells and yet, in pernicious anaemia the number of G cells is markedly increased, while in one of the patients with carcinoid tumour, the cells of the neoplasm contained (and presumably secreted) gastrin.⁶⁵ Unless gastrin exerts a positive feed back effect on its own cells of origin (which seems unlikely), it is probable that some other trophic agent is involved in the hyperplasia and neoplasia of the endocrine cells of the gastric mucosa during achlorhydria.

Alternative treatments for preventing relapse of ulcers

It has been argued that in view of the hypothetical risks associated with the continuous use of gastric secretory inhibitors these drugs should not be used in the long term treatment of ulcer disease.

Unfortunately, there is no satisfactory alternative.

(1) The most important treatment with proven capacity to induce sustained remission of ulcers is gastric surgery. It is therefore necessary to emphasise that, while the development of gastric cancer during treatment with drugs is only conjectural, gastric cancer is a confirmed consequence of gastric surgery. The gastric mucosa is very abnormal after gastric surgery,^{67 68} which presumably contributes to the high incidence of cancer of the gastric remnant after gastrectomy in experimental animals.⁶⁹⁻⁷¹ Moreover, as the entero-anastomosis is the site of the most marked proliferation, it is not surprising that carcinomata often arise at, or near, it.⁷² The incidence of gastric cancer after gastric operations has been the subject of numerous reports with contradictory conclusions and equally contradictory and often dogmatic statements concerning the presence of increased cancer risk. Opinions range from 'no increased risk', with an incidence of gastric cancer after gastric operations not greater than control^{73 74} (perhaps in part because patients die from diseases related to smoking⁷⁵) to conclusions suggesting that the increased risk is real, but does not warrant screening.⁷⁶ Even the view that the increased risk needs repeated monitoring to detect preneoplastic, or frankly neoplastic lesions,^{77 78} with subsequent prophylactic gastrectomy has been put forward.

To summarise, therefore, the incidence of gastric cancer after gastrectomy differs in different parts of the world, some reported values reaching 21%.^{78 79} The incidence of gastric cancer after vagotomy is now being studied, but experimentally vagotomy predisposes to gastric cancer.⁸⁰⁻⁸² A 2% incidence of gastric cancer after vagotomy has been recorded in patients,⁸³ with an incidence of 2.2% after vagotomy and drainage,⁸⁴ while about 2% of one series of patients with gastric cancer had previously had vagotomy.⁸⁵ Even so, cancer ranks low in the list of causes of mortality after gastric surgery.

It is of course not surprising that controversy surrounds the incidence of gastric cancer after operations for ulcer disease. It is probably correct to conclude that gastric operations invariably render the gastric mucosa more susceptible to carcinogens. The actual incidence of gastric cancer will depend on the severity of the proliferative changes of the gastric mucosa (as 'initiated' cells may be desquamated if the degree of proliferation is too severe), as well as on the exposure of the abnormally proliferating gastric mucosa to organ-specific genotoxic carcinogens. The presence and concentration of this type of carcinogen almost certainly varies greatly in different geographic areas and perhaps even in the same individual at different

times and circumstances. The assessment of increased risk after gastric operations is further confounded by the statistical comparison of the incidence of gastric cancer in operated individuals with the risk in the 'control' general population. It seems likely that this type of analysis is potentially misleading, because the gastric mucosa of patients with duodenal ulcer is 'resistant' to the development of gastritis,⁸⁶ so that gastric cancer in unoperated patients with duodenal ulcer is very rare,⁸⁷ while the incidence of gastritis in the general population is high and increases with age.⁸⁸ As atrophic gastritis predisposes to gastric cancer, comparison of the incidence of gastric cancer after gastric operation for duodenal ulcer with the incidence in the 'general population' mistakenly results in the comparison of two groups of individuals with potentially premalignant mucosa rather than valid comparison with the 'true' control of long standing, unoperated duodenal ulcer disease. The latter comparison has not yet been made. It is not surprising, however, that a recent report notes that the risk of developing gastric cancer after operation is greatest in young patients⁸⁹ – that is, the comparative risk is greatest when young postoperative patients are compared with young 'normal' controls who have not yet developed atrophic gastritis.

(2) As a further alternative mode of therapy, it has been suggested that the potential hazards of H₂ histamine receptor antagonists and other gastric secretory inhibitors can be avoided by using drugs such as antacids and sucralfate, which are considered to act directly on the ulcerated mucosa of the stomach or duodenum. Most of the antacid preparations available at present, as well as sucralfate, contain aluminium and as aluminium compounds tend to bind phosphate in the gut lumen,^{90 91} long term administration results in damage to bone.^{92 93} Potentially more serious is the fact that aluminium is absorbed from antacid preparations^{93 94} and from sucralfate^{90 95 96} and is therefore potentially capable of exerting adverse effects on other tissues, especially the nervous system, if retained in the body (as happens in experimental animals).^{97 98} For example, aluminium increases the permeability of the blood brain barrier to peptides affecting the nervous system.⁹⁹ In addition, aluminium is neurotoxic and when deposited in cerebral tissues, remains there.¹⁰⁰ It is interesting to note the observation that large amounts of aluminium occur in the brain of patients with Alzheimer's disease¹⁰¹⁻¹⁰³ and it has been proposed that the aluminium is causally implicated in the development of the dementia. It has also been denied, however, that aluminium concentrations in cerebral tissue are abnormally high in patients with

Alzheimer's disease.^{104 105} In view of the discord and of the possibly serious unwanted effects of prolonged administration of aluminium-containing drugs, it is surprising that there are so few published reports of studies in appropriate animal models. Administration of aluminium hydroxide does not significantly increase the intracerebral aluminium content of rats, although aluminium citrate does.¹⁰⁶ It has to be borne in mind, however, that the rat (unlike the cat, dog, and rabbit) is much more resistant to aluminium-induced neurotoxicity,^{104 107} although long term administration of aluminium chloride produces behavioural changes in two strains of rats without overt signs of ill health of the animals.⁹⁷ The controversy surrounding the neurotoxicity of aluminium and its implications for man demands attention from drug-regulatory agencies in order to clarify whether, or not, it is safe to use aluminium-containing drugs for the long term treatment of ulcer disease.

(3) A number of prostaglandin derivatives have been studied in ulcer healing trials. These drugs are thought to act topically on the gastric and duodenal mucosa and also to inhibit gastric secretion. In view of the reports that some prostaglandins stimulate rat gastric mucosal proliferation,¹⁰⁸ careful studies of their effects on gastric carcinogenesis are necessary, before these drugs are used clinically for the maintenance of ulcer remission. Such proliferation might promote gastric carcinogenesis, especially in view of reports that the E₂ and F_{2α} derivatives exert cocarcinogenic effects on other tissues.¹⁰⁹

Conclusion

Four gastric secretory inhibitors have produced four different types of gastric hyperplasia and neoplasia in rats. This experimental finding – that the target organ of the four drugs has selectively undergone neoplastic change during administration of the drugs – is a cause for concern, despite the obvious proviso that the gastric neoplasms have developed in animals and not in man. There are, of course, marked differences in the sensitivity of different species even to powerful genotoxic carcinogens like nitrosamines.^{110 111} Moreover, the connection between the development of cancer in rats and the possibility of a similar neoplastic change under similar circumstances in man is not a matter of simple extrapolation, but requires proof (or rejection).^{112–116} Until it is possible to refute this risk, however, it is probably advisable not to use for long term therapy any drugs that produce site-specific neoplastic change in animals. Fortunately, in cimetidine and ranitidine we do appear to have drugs which have been shown to be safe in animals

and which can be, and have been, given to patients safely.

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