*Leading article***There is more to healing ulcers than suppressing acid**

The finding that a given acid output might be associated with a normal stomach, or with an ulcer, has stimulated only modest interest in factors such as pepsin and the mucosal barrier, as recently discussed in these columns by Mr Venables.¹ This is because it is difficult to make objective measurements, (especially in man) of the mucosal barrier² and even of pepsin.^{3,4} The mucosal barrier is a theoretical concept dealing with the ability of the mucosa to resist digestion by acid and pepsin. There are many factors involved in preserving an intact epithelium: mucus and its adherence to the epithelium, bicarbonate secretion deep to the mucus, epithelial cellular integrity, hydrophobicity, mucosal blood flow and interstitial bicarbonate. These factors have been extensively reviewed by several authors,^{2,5–7} and so will not be discussed further.

Pepsin is also important but comprises several proteolytic enzymes which have slightly different characteristics such as varying pH for optimal activity,⁸ with a predominance of pepsin I secretion in duodenal ulceration. Pepsin secretion is substantially increased in duodenal ulcer patients.⁹ In patients whose ulcers do not heal with cimetidine there is not only poor suppression of acid secretion, but an even smaller reduction in pepsin output.¹⁰ On the other hand attempts to correlate pepsin with ulcer activity and individual response to cimetidine have been disappointing¹¹ and inhibition of peptic activity by amylopectin sulphate has not proved advantageous in healing duodenal ulcers.¹²

Against this uncertain background Baron *et al*, have investigated the effect of colloidal bismuth (De-Nol) on gastric acid, pepsin and mucus and report their findings in this issue of *Gut*.¹³ Their most striking observation was a decreased concentration and output of pepsin. Of particular interest is the observation that the measurements were done 24 hours after the last dose of colloidal bismuth, suggesting a sustained effect on the mucosa – it would be very interesting to know how long this effect lasted. A previous study by Hollanders *et al*¹⁴ suggested that De-Nol produced its therapeutic effect by a change in the character of mucus. This was not confirmed by Baron *et al*,¹³ but their technique measured aspirated mucus while Hollanders' group¹⁴ measured changes in types of mucus in biopsy samples. Mucus which is adherent to the mucosa is probably more important, as it maintains a pH gradient.² It could be argued that improved adherence of mucus to the mucosa after treatment due to diminished peptic digestion might account for the modest decrease in mucus aspirated by Baron *et al* – clearly more work is needed in this interesting area.

Colloidal bismuth has been available for many years and is effective in healing ulcers^{15,17} – the drug was reviewed by Tytgat *et al*.¹⁵ Bismuth does not inhibit secretion of acid (confirmed by Baron *et al*¹³) but inhibits pepsin

in vitro and chelates to the proteinaceous material at the base of an ulcer. Colloidal bismuth binds to pepsin and complexes with protein and mucoglycoproteins to provide an additional diffusion barrier to acid, an effect only found with this drug, and not with other bismuth compounds. It has been suggested that colloidal bismuth restores the duodenal mucosal cells closer to normal than after treatment with cimetidine,¹⁶ but this needs confirmation. Ulcers which fail to heal with cimetidine heal more effectively with colloidal bismuth^{17 18} and it is probable that the subsequent relapse rate of duodenal ulcers is lower¹⁹ than that after cimetidine²⁰ or ranitidine.²¹ The mechanism is unknown, but possible explanations could be a sustained decrease of pepsin, persistence of bismuth in the body, or an effect on the microflora of the stomach and duodenum. Marshall *et al*²² found *Campylobacter*-like organisms in association with antral gastritis and with peptic ulcers.^{22 23} These organisms are sensitive to bismuth²⁴ which raises another possible mechanism of action for colloidal bismuth. Colloidal bismuth has few adverse effects, but it darkens the stool (and so can mimic melaena) and has an unpleasant aroma in liquid form. The chewable tablet is comparable in efficacy,²⁵ but can darken the teeth. Bismuth neurotoxicity is rare, but may occur in the presence of renal failure, or possibly with continuous medication. If the mechanism of action of colloidal bismuth can be established, it should throw considerable light on peptic ulcer disease.

Sucralfate is the other mucosal protective agent used to treat ulcers – it has been reviewed in detail by Brogden *et al*.²⁶ Its mode of action is also being explored. Sucralfate binds selectively to ulcerated tissues; it also binds bile and pepsin and reduces peptic activity *in vivo*. Despite the presence of aluminium in the compound it is not an antacid, but stimulates bicarbonate secretion by the mucosal cells²⁷ and increases gastric release of prostaglandin E₂.²⁸ It seems probable that some of sucralfate's actions are mediated by prostaglandins.²⁹

Healing rates with sucralfate given to patients with duodenal ulcer have usually been significantly better than placebo and comparable with cimetidine,¹⁵ but results in gastric ulcers are less convincing.^{26 30} Sucralfate is given as 1 g four times daily or 2 g twice daily³¹ and it has been claimed that combination treatment with cimetidine speeds healing compared with either drug alone³² but this small trial needs confirmation. Sucralfate taken 1 g twice daily appears to decrease the relapse rate of DU³³ and 1 g in the morning/2 g at night decreased the relapse rate of GU.³⁴ Larger studies are needed to evaluate fully the data on sucralfate in maintenance therapy and in decreased posthealing relapse rate.³⁵

Prostaglandins (PGs) have aroused great interest because of their mucosal protective properties – comprehensively reviewed by Hawkey and Rampton.³⁶ Prostaglandins influence several aspects of the mucosal barrier – bicarbonate secretion, mucosal blood flow and repair mechanisms within the mucosa. Misoprostil and enprostil, however, the two PG analogues at present undergoing clinical trial, also inhibit acid secretion. The dual action of acid inhibition³⁷ with a postulated enhancement of mucosal protection is most attractive, but disappointingly the healing rates published so far do not suggest an advantage over histamine H₂ receptor antagonists.^{38 39} Misoprostil and enprostil can cause diarrhoea and potentially can cause abortion, so that their place in therapy will need

careful assessment. Their use in patients who are on non-steroidal anti-inflammatory drugs is particularly attractive, but evaluation is at an early stage.

Other drugs with main action outside the secretion of acid have been used. The selective muscarine antagonist, pirenzepine, inhibits acid¹⁵ but chiefly it decreases pepsin, especially vagally stimulated secretion.⁴⁰ Pirenzepine is comparable with cimetidine in healing rates¹⁵ and may lower the relapse rate of DU when given as a single night-time dose.⁴¹ Unwanted effects are common – usually a dry mouth or blurred vision,⁴² but this is not a problem with the night-time dose used for maintenance therapy.⁴¹ Carbenoxolone also has several actions and heals ulcers without affecting the output of acid – it inhibits pepsin⁴³ and prolongs the life span of epithelial cells.⁴⁵ Carbenoxolone is one of the drugs which influences mucus secretion,⁴⁴ possibly acting through prostaglandins.⁴⁶ The mineralocorticoid effects of carbenoxolone have limited its clinical use.

A deglycyrrhizinized liquorice/antacid preparation (Caved-S) has been found useful in limited trials⁴⁷ but there is no information on the pharmacology of the many substances in the liquorice extract. Trimipramine, used in Scandinavia, is a tricyclic antidepressant with a weak anticholinergic effect, so that it modestly suppresses acid and pepsin. Healing rates are better than placebo but inferior to cimetidine.¹⁵ Unwanted effects of dry mouth and tiredness limit its use.

Although we look to drugs either to control acid secretion, or to improve the mucosal defences, we must not forget that diet may have therapeutic actions. It has become fashionable to underrate diet as a factor in ulcer disease. Although diet has no value in the short term healing of ulcers⁴⁸ a comparison of high and low fibre diets showed that relapse rates were lower in patients on high intake of dietary fibre.^{49, 50} Lipid soluble substances in certain foods are protective against experimentally induced ulcers.⁵¹ Recently the essential fatty acid, linoleic acid, has been found to have a protective action,⁵² which may be mediated through prostaglandins.

What then is the place of drugs which do not suppress or neutralise acid in the treatment of peptic ulceration? The two available drugs which are in this category are colloidal bismuth and sucralfate. Both have healing rates comparable to the H₂ receptor antagonists and so can be used as alternatives for short term healing. Short term healing is not usually difficult, however, as over 90% of ulcers will heal with eight weeks' treatment. The problem is keeping the ulcer healed. The medical options are for intermittent therapy when the ulcer relapses, or regular night time maintenance treatment. Experience with maintenance treatment using histamine H₂ receptor antagonists is vast and this gives them a clear advantage when compared with colloidal bismuth (where maintenance should not be used), or sucralfate. Concern has been expressed, however, over potential risks from suppressing acid secretion over long periods.⁵³ The concern is that bacteria will colonise the stomach and produce potential carcinogenic substances from nitrates and nitrites in the diet. With very powerful acid-suppressing drugs such as omeprazole very long term treatment must be a cause for some concern, but with histamine H₂ receptor antagonists the inhibition of intragastric acidity is limited to several hours each day, making the theoretical risk very small. Furthermore, the histamine H₂ receptor antagonists have been found to be very

safe in clinical practice,⁵⁴ which now extends to 10 years with cimetidine. Clearly no complete assurance can be given on this point until further experience is gained and surveillance continued.

Colloidal bismuth probably does produce a lower relapse rate after a short course of treatment, but this is unlikely to be very important in the management of individual patients, because most (62%) relapse by the end of one year: a gain of only 27% over ranitidine.²² Nonetheless, infrequent short courses of colloidal bismuth are a reasonable treatment schedule, provided renal function is good – maintenance treatment should not be given. Sucralfate is safer than colloidal bismuth for long term treatment, but needs to be taken at least twice a day and so far maintenance data are meagre.

Although it is unlikely that these alternatives to histamine H₂ receptor antagonists will replace them for routine or maintenance treatment of peptic ulcer, they do offer a useful alternative in some situations. Continued investigation of their mode of action may enhance our understanding of the defensive processes of the gut mucosa. This is a desirable objective, because it may eventually enable us to devise ways of changing the natural history of ulcer disease, something which the mere inhibition of acid secretion has failed to do.

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