Leading article

Duodenal ulcers that will not heal

Why is it that approximately 20% of duodenal ulcers fail to heal after one month of treatment with an active drug? This failure rate is relatively constant, regardless of whether duodenal ulcers have been treated with cimetidine, ranitidine, antacids, pirenzepine, tripotassium dicitrato bismuthate, sucralfate, or carbenoxolone.

There are two likely explanations for treatment failure in acute duodenal ulceration: either the type of treatment is inappropriate, or it is not strong enough. These two possibilities have been explored in three papers in this issue of Gut.1-3

Refractory Duodenal Ulcer

Dr Bardhan provides another report concerning his extensive experience with cimetidine in the treatment of duodenal ulceration.1 4 5 Using cimetidine 1 g/d, 78% of 495 episodes of duodenal ulceration had healed after one month; 83% and 93% had healed after two and three months on the same treatment, respectively. During a period of four years, he identified 66 patients with a ‘refractory’ duodenal ulcer that had not healed after three months of treatment with cimetidine 1 g/d. These patients continued to receive cimetidine with the dose sometimes doubled or trebled. In the end (average 7.4 months) 56% did heal, but the remainder did not, despite an average of 9.4 months of treatment with cimetidine.

The reasons why these patients failed to respond to cimetidine are not clear. As a group they tended to have larger duodenal ulcers associated with more severe duodenitis, than those who responded promptly to cimetidine. They tended to be younger, yet had a longer ulcer history. The H2-antagonist was absorbed adequately, but increasing doses of the drug did not cause increasing inhibition of pentagastrin stimulated acid secretion. In nine patients receiving cimetidine 3 g/d, pentagastrin stimulated secretion was decreased by an average of only 28% two to three hours after a 600 mg dose of cimetidine by mouth: these patients appear to be genuinely resistant to cimetidine’s antisecretory action.

The most obvious conclusion from Dr Bardhan’s paper is that most duodenal ulcer patients respond promptly to a short course of treatment with a conventional dose of cimetidine. If two to three months of treatment do not heal an ulcer, however, cimetidine should be stopped and something different given to the patient.

Trying something different – bismuth

There are few centres with enough clinical experience to collect sufficient cimetidine failures to try something different. Dr Lam and the Combined Gastrointestinal Unit in Hong Kong reviewed 212 duodenal ulcer patients after four weeks of treatment with cimetidine 1 g/d.2 Twenty five of these
patients had ulcers which showed little, or no sign of healing: these patients were randomly allocated to receive either tripotassium dicitrato bismuthate, one tablet four times a day before meals, or a higher dose of cimetidine – 400 mg qds. If the duodenal ulcer had not healed after a further four weeks, the bismuth and cimetidine were switched. Overall, 85% of cimetidine resistant ulcers healed during treatment with tripotassium dicitrato bismuthate, whereas only 40% of the low dose cimetidine failures healed when the dose was increased.

This important study suggests that in patients not responding to cimetidine control of acid may be less important than ‘mucosal protection’. Conversely, it is quite possible that cimetidine may be effective in those 20% of ulcers that fail to heal after an initial course of treatment with bismuth.

Unfortunately it is unclear how tripotassium dicitrato bismuthate works. Although it does adhere to the raw surface of an ulcer,6 this ‘Band-Aid’ action seems unlikely to protect from acid and pepsin attack.

Does tripotassium dicitrato bismuthate have some effect on the regeneration and integrity of the duodenal mucosa? There are two pieces of evidence to suggest that it has activity other than the proposed ‘Band-Aid’ action. Firstly, the microvilli of epithelial cells in the duodenal mucosa return to their normal height under the influence of bismuth, but not cimetidine.7 Secondly, a short course of bismuth may be followed by a lower ulcer relapse rate than after a short course of cimetidine in the 18 months after initial ulcer treatment,8 but this benefit has not been confirmed.9 It is difficult to understand how a ‘Band-Aid’ action would provide long term protection from recurrent ulceration.

It is now clear that a short period of treatment with tripotassium dicitrato bismuthate does cause accumulation of bismuth in the body. At the end of six weeks of treatment with tripotassium dicitrato bismuthate tablets, median urinary bismuth concentration had risen 48-fold, and there was still a 10-fold rise two weeks after stopping the tablets.10 This bismuth accumulation was not reflected in a major change of serum bismuth concentration. It could be rewarding to measure bismuth in human tissue using a method similar to that used for assessing tissue zinc content11 before and after a course of bismuth. It is possible that bismuth has a role in the maintenance of mucosal repair and a short course of treatment may provide a depot of bismuth, which gives some months of protection against relapse.

The Hong Kong study shows for the first time a successful strategy for the minority of patients who do not heal promptly during a short course of cimetidine – most of these patients can be expected to respond to tripotassium dicitrato bismuthate.

MAKING H₂-ANTAGONISTS MORE ACTIVE
When Dr Bardhan's patients failed to respond to cimetidine 1 g/d he increased the dose two or three-fold, without obvious benefit.1 In Hong Kong, the dose of cimetidine was increased from 1·0 to 1·6 g/d with only 39% of cimetidine resistant ulcers healing in the next four weeks.2 Increasing the dose of cimetidine does not cause a dramatic increase in the drug’s antisecretory effect.12-14 The peak blood concentrations of cimetidine after a 200 mg dose are already in the upper part of the dose
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response curve, hence even higher blood concentrations of cimetidine are not accompanied by a proportionately greater inhibition of stimulated gastric acid secretion.

Ranitidine 150 mg twice daily does have a greater antisecretory effect than cimetidine 1 g/d. Compared with placebo in duodenal ulcer patients, cimetidine 1 g/d causes intragastric 24 hour median pH to rise from 1·4 to 1·7, but ranitidine 150 mg bd causes a rise from 1·4 to 2·4. cimetidine causes a two-fold decrease of acidity and ranitidine a 10-fold decrease, yet it appears that these doses are equally effective for the acute treatment of duodenal ulceration.

Nocturnal acidity is obviously very important in duodenal ulcer disease. Cimetidine 400 mg given at night, which only lowers intragastric acidity for perhaps eight hours, protects most patients against relapse of ulcer. A recent preliminary report has suggested that ranitidine 300 mg at bedtime is at least as good as ranitidine 150 mg bd. Taking both tablets of ranitidine at bedtime will provide greater control of nocturnal acidity, with little effect in the second half of the following day. Does control of daytime acidity matter? Is compliance with a simple nocturnal regimen more important?

One way of getting an extra antisecretory effect using an H2-antagonist is to add an effective dose of an anticholinergic, where there is some definite evidence of additional benefit, or even synergy. The addition of pirenzepine to an H2-antagonist could provide a potentially powerful antisecretory combination, which may be useful for patients who do not respond to conventional doses of an H2-antagonist.

Finally, optimal precipitation of bismuth from tripotassium dicitrato bismuthate occurs when intragastric pH is between 2·5 and 3·5. As median 24 hour intragastric pH is 1·4 in untreated duodenal ulcer patients, maximal 'Band-Aid' activity might occur during simultaneous treatment with tripotassium dicitrato bismuthate and an H2-antagonist.

Omeprazole – the strong one

Omeprazole is a substituted benzimidazole compound which decreases acid secretion by inhibition of the parietal cell's proton pump H+K+-ATPase. On page 707, Howden, Forrest, and Reed report that in healthy volunteers six to eight hours after a single oral dose of omeprazole 60 mg there is a 95% decrease of pentagastrin stimulated acid output. There is almost 100% inhibition of stimulated acid secretion at a similar time after the seventh daily dose of omeprazole 60 mg.

Omeprazole 30 mg/d is the optimal dose for a maximal decrease of 24 hour intragastric acidity in duodenal ulcer patients, causing median 24 hour pH to rise from 1·4 to 5·3. Not only is the drug a powerful inhibitor of gastric acid secretion, but it is active for a long time after it is no longer detectable in the blood. In nine duodenal ulcer patients, seven days after the last of 14 doses of omeprazole 30–60 mg/d, there was still a significant 26% decrease of 24 hour intragastric acidity.

In terms of a potentially useful ulcer healing drug, omeprazole appears to have four advantages: firstly, it causes a profound decrease of acid secretion, stronger than any of the presently available single drug regimens; secondly, by raising median pH from 1·4 to 5·3, pepsin is stable.
but essentially inactive; thirdly, the drug can control 24 hour acidity with one dose each day, which should help compliance; finally, the drug is active for many days, hence a patient's omission of even several days' doses need not interrupt control of gastric acidity.

Is omeprazole particularly good for the treatment of duodenal ulceration? Can omeprazole eliminate the 20% one month failure rate recorded with other medical treatments? Can omeprazole heal ulcers in two weeks? We still do not know. The results of three dose comparative studies suggest that omeprazole can provide complete and rapid healing of duodenal ulceration,26-28 but these remarkable results could just be beginners' luck.29 We must wait for the results of controlled trials.

What could be the disadvantages of profound inhibition of gastric acid secretion? Firstly, omeprazole does trigger a rise in fasting plasma gastrin concentration with a four-fold rise after two weeks of treatment, returning to normal 10 days after stopping the drug.25-30 Treatment of healthy volunteers with omeprazole 40 mg/d for 14 days, however, does not increase parietal cell mass, as assessed by serial pentagastrin tests.31 Indeed, if gastrin does have a trophic effect on the epithelium of the duodenum,32-33 a modest rise of plasma gastrin concentration could help ulcer healing. Secondly, gastric acid protects the lower bowel from pathogens and it is possible that patients with virtually no gastric acid may be more liable to enteric infections such as typhoid,34 brucellosis,35 giardiasis,36 cholera,37 and even pseudomembranous colitis.38 Finally, it has been shown in volunteers that after 14 doses of omeprazole 30 mg/d the intragastric bacterial count and also the nitrite and N-nitrosamine concentrations rise significantly; three days later, after stopping the treatment with omeprazole these changes had resolved.39

For the first time the physician can induce virtual anacidity by using omeprazole. Will no acid mean 100% no ulcer? If so, will the best long term strategy for the duodenal ulcer patient consist of intermittent pulses of drug induced anacidity at times of ulcer relapse, or induction of ulcer remission followed by long term treatment with a milder antisecretory regimen? Eight years after the 'cimetidine revolution', there still seem to be more questions than answers.

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References

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