Relapse rates after duodenal ulcer healing – apples or pears?

sir.—The one year maintenance study reported by Bardhan et al (Gut 1988; 29: 1748–54) showed Maalox TC, given in a dose of 3 tablets (81 mmol acid neutralising capacity) twice daily, to be as effective as cimetidine 400 mg nocte in the prevention of duodenal ulcer relapse; both these agents were significantly better than placebo. The relapse rate of only 57% in their placebo treated group, however, contrasts rather strikingly with the 75 to 90% relapse rates reported in most other studies; the relapse rate in their cimetidine treated group was also somewhat low. Their low relapse rates are more comparable with those of Sontag et al who noted one year relapse rates of 50% on placebo and 28% on cimetidine maintenance therapy. Dare one speculate on the discrepancy between the relatively low relapse rates in these two studies compared with most others?

There is good evidence that six to 12 month relapse rates after initial duodenal ulcer healing with a colloidal bismuth agent, or sucralfate, tend to be lower than those after healing with an H₂-receptor blocker.¹ One year relapse rates after colloidal bismuth healing, however, are usually in excess of 60%. In any event the duodenal ulcers in over 90% of the patients in Bardhan et al’s study were healed on an H₂-receptor blocker and it is probable that the same applies to those patients drafted into the Sontag study.

Attention has recently been focussed on the speed of relapse in patients on placebo after treatment with an ulcer healing agent. Most maintenance studies allow for routine endoscopies at six and 12 months and it is common cause that the majority of relapses occur during the first six months. A few studies allow for routine endoscopies at four, eight, and 12 months and, in these, relapses within the first four months account for well over 60% of the total number of relapses at one year. This applies particularly to patients after initial healing with an H₂-receptor blocker. Lee et al, in a one year study in patients after healing with ranitidine (n=54) or a colloidal bismuth preparation (n=53), reported that no fewer than 40 (83%) of the 48 relapses in the ranitidine healed group occurred within the first four months. This compared with 22 (67%) of the 33 relapses in patients treated initially with colloidal bismuth. It should be stressed that the four month relapse rates in this study were 74 and 41% respectively.

More recent studies have confirmed the rapidity of early relapse in patients after healing with an H₂-receptor blocker. In the first, ulcer healing was documented after six weeks treatment with either ranitidine or sucralfate in 32 duodenal ulcer patients. Active treatment was discontinued, and a routine endoscopy carried out four weeks later. An ulcer relapse was noted in 10 of 15 ranitidine healed and in three of 17 sucralfate healed patients. Boyd et al, on the other hand, carried out monthly endoscopies in 34 patients admitted to a maintenance ranitidine study immediately after duodenal ulcer healing by ranitidine. The cumulative relapse rate at one year was 48% with more than half of the first recurrences occurring within the initial two months. The majority of endoscopic recurrences, it would seem, develop within the first few months after duodenal ulcer healing.

It is not known whether the duodenal ulcers which relapse within one or two months of endoscopic healing occur in patients with a more aggressive form of the disease. What is clear, however, is that commencing a maintenance study a month or more after documented healing automatically excludes a substantial proportion of early relapers. Most maintenance studies do in fact commence within a few days of endoscopic healing of a previously active ulcer. Neither Bardhan et al nor Sontag et al had recent ulcer healing as a criterion for entry into their maintenance studies. Bardhan et al studied ‘patients with previous symptomatic endoscopy proven DU which had been shown endoscopically to have healed within the previous one year, provided they were asymptomatic and ulcer free at endoscopy done less than seven days before commencing (maintenance) treatment’. The mean time interval between healing of the last ulcer and entry into the study was 51 days. In similar vein, Sontag et al required their patients to have ‘a history of duodenal or channel ulcer diagnosed by endoscopy or unequivocal x-ray findings within the previous two years, with at least one episode of recurrent characteristic ulcer symptoms during the year preceding entry. Endoscopy was performed at entry, and only patients with a normal duodenal mucosa were included’. It follows that both protocols would have resulted in the exclusion of a large proportion of patients with a tendency to early relapse, and that this probably accounts for the seemingly lower relapse rates in these studies.

The above comments should not be construed as a criticism of either of these studies. Both Bardhan et al and Sontag et al presented their entry criteria in
meticulous detail, and the superiority of a potent antacid, or cimetidine, over placebo is not in question. There is, however, the problem of translating the absolutes of controlled trials into the therapeutics of peptic ulcer. The design of both studies favoured exaggerated remission rates for active and placebo therapy, and it is unlikely that similar rates would have been achieved had patients been enrolled on ulcer healing.

Double blind randomised, placebo controlled maintenance studies, embalmed by a plethora of data on frequency of routine endoscopy, definition of ulcer recurrence, asymptomatic recurrence, smoking, duration of disease, previous active therapy etc. have, over the years, assumed an almost unchallengeable mystique. The list of variables, however, is an evolving one. _Campylobacter pylori_, parietal cell sensitivity on ulcer healing, parietal cell sensitivity levels have recently been suggested, and to these must now be added the time interval between recent ulcer healing and entry into study. As the majority of recurrences occur within the first few months after ulcer healing, we would suggest that the time interval between healing and entry be considered before trying to compare apples with pears. Ideally, maintenance studies should only include patients enrolled immediately after endoscopic healing and withdrawal of the healing agent.

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References


Disturbed fibrinolysis in patients with inflammatory bowel disease

str.—The potentially important findings reported by Dr de Jong and colleagues (Gut 1989; 30: 188-94) on fibrinolytic abnormalities in inflammatory bowel disease patients are diminished in value by misuse of statistical methods. It is claimed that the finding of a median prothrombin time of 18 s (normal range 15-19 s) in patients is so different from the median prothrombin time of 17 s in controls that such a difference would not be expected by chance if the experiment were repeated 1000 times. In a study of 28 patients with great overlap between the two groups this is clearly nonsensical.

In Fig. 2 where the actual data for plasminogen activator inhibitor are shown the groups appear to be virtually identical: indeed if one performs a Wilcoxon’s rank-sum test on the points there is no difference between the two groups (T1=724, T2=872), though a level of significance p<0.01 is claimed.

The same considerations apply to other aspects of the data as presented and this renders the conclusions of the study invalid.

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Rebound nocturnal hypersecretion after H2-receptor antagonist

str.—The recent paper by Fullarton et al gives rise to some important criticism. There are three major points to emphasise: (1) The small number of patients (eight) and the marked individual variation of their secretory patterns (see the non-homogeneous nocturnal acid output values in the pretreatment phase) reduce the reliability of the study. This is particularly so when considering that, by simply adding two cases to the six patients of the authors’ interim report, median pH values of the three daytime profiles changed dramatically – for example, from pH 0-7 to pH 1-3 on treatment, and
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