Relapse of duodenal ulcer: does it matter which drug is used in initial treatment?

Duodenal ulcers recur within a year in 80-90% of patients treated initially with $H_2$ antagonists, and evidence now exists that relapse rates may be lower after treatment with other ulcer healing drugs. Moshal postulated in 1978 that relapse rates might be lower after treatment with tri-potassium di-citrato bismuthate (Moshal MG, Sixth World Congress of Gastroenterology, Madrid, 1978), and in a double blind prospective study we showed that this was indeed so. McLean and others have concluded that this may also be true for other ulcer healing drugs, including antacids, anticholinergics, antacid and anticholinergic combinations, carbenoxolone, sucralfate, and trithiolazine.

Evidence for a reduction in relapse rate relative to cimetidine is not, however, strong for most of these agents individually. The studies have often been small, and the differences have also been small, either failing to reach significance or doing so only transiently. For example, Hansky and others claimed no significance for the difference in relapse rates that they observed in a small study of antacids against cimetidine, and larger studies have found no difference. The strength of the argument of McLean and others is, however, that when an appreciable difference in relapse rates is observed it is consistently in favour of the comparative agent and to the detriment of cimetidine.

Only in the case of tri-potassium di-citrato bismuthate is there sufficient evidence for a single drug that the effect is real. Although our initial study was not immediately confirmed, four subsequent trials have shown lower relapse rates after tri-potassium di-citrato bismuthate than after an $H_2$ antagonist. The more recent of these studies strengthen the case made by McLean and others and extend it to include ranitidine, which is followed by a similar relapse rate to cimetidine. The consistency of the results leaves little doubt that the phenomenon is genuine, and in a further trial recurrence rates were similar in patients maintained on cimetidine and those given only a short course of tri-potassium di-citrato bismuthate to induce healing.

Combining results from the six studies showed that 85% of patients treated with $H_2$ antagonists relapse within a year compared with 59% of those treated with tri-potassium di-citrato bismuthate. Combining data from clinical trials is unreliable, but this is the best available quantitative estimate of the difference between the treatments. Because duodenal ulceration is so common even a difference of about 25% has important implications. Using life table analysis, however, probably underestimates the real difference between the treatments in terms of morbidity, time, and cost because patients who relapse are not (usually) dead. They are simply withdrawn from the trial and require further treatment, which will often be another course of drugs or some form of maintenance. Maintenance treatment is effective but because of the cost is likely to be reserved for patients who relapse rapidly and predictably and for certain high risk groups.

We have applied an analysis similar to that of McLean and others to the data from the six studies and calculated the relapse rates after healing with an $H_2$ antagonist (17% a month) and with tri-potassium di-citrato bismuthate (7% a month). Using these rates we have investigated the implications of a policy of repeated courses of treatment with the same agent—either an $H_2$ antagonist or tri-potassium di-citrato bismuthate—when a patient relapses. After a short time a steady state is reached in which 19% of the $H_2$ antagonist group are on treatment but only 10% of the tri-potassium di-citrato bismuthate group. Twice as much $H_2$ antagonist will thus be used, which would double the costs with cimetidine and triple them with ranitidine at current non-contract prices. Furthermore, at any time more patients on $H_2$ antagonists have an ulcer, although they will not necessarily be symptomatic.

This model may not reflect accurately clinical practice and may apply more to the artificial context of the clinical trial. Nevertheless, it probably gives a better idea of clinical practice than the usual life table analysis. Outside clinical trials patients who undergo asymptomatic relapse are unlikely to be diagnosed or treated. This will reduce the overall costs of drug treatment, but the differential costs may still apply unless asymptomatic relapse is much less common after tri-potassium di-citrato bismuthate than after an $H_2$ antagonist.

The reason for the difference in relapse rates is unknown. The notion that $H_2$ antagonists heal more "difficult" ulcers that are also more prone to relapse is not tenable since the healing rates in the six studies were actually slightly higher with tri-potassium di-citrato bismuthate than with the $H_2$ antagonists. Rapid relapse after an $H_2$ antagonist might be explained by rebound hypersecretion secondary to previous suppression of acid secretion leading to hypergastrinaemia and increased parietal cell mass. Although increases in serum
gastrin concentration during treatment with H2 antagonists has often been reported, there is little evidence of rebound hyperscretion and increased parietal cell mass.33 Recently, however, increased sensitivity of the parietal cell after ranitidine treatment to the submaximal and more physiologic stimulus of simulated feeding has been reported.33

The difference in relapse rates may relate to the duodenal mucosal cell failing to return to normal after an H2 antagonist but not after tri-potassium di-citrate bismuthate.33 This requires confirmation, and even if true the mechanism remains to be determined. The relation between Campylobacter pyloridis, gastritis, and peptic ulceration might be relevant.33 Tri-potassium di-citrate bismuthate seems to remove Campylobacter pyloridis from gastric mucus whereas H2 antagonists do not.33 A further suggestion33 is that because of accumulation within the body bismuth continues to be excreted after tri-potassium di-citrate bismuthate is stopped.33 If correct this would imply a systemic and not just a local effect on ulcer healing. It also raises the spectre of bismuth encephalopathy, but this has not been reported with tri-potassium di-citrate bismuthate, which is recommended for four to eight weeks course to heal ulcers and not for prolonged maintenance.

The higher relapse rates after healing with H2 antagonists compared with tri-potassium di-citrate bismuthate (and perhaps other agents) is now well established and should probably influence prescribing. Furthermore, a large scale trial to test the predictions of our model seems worthwhile.

J PAUL MILLER
Consultant gastroenterologist
E BRIAN FARAGHER
Senior medical statistician

Department of Medicine,
University Hospital of South Manchester,
Manchester M20 8LR

Correspondence to: Dr Miller.

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A plan for paediatric surgery

The Department of Health and the surgical establishment have now accepted the need to improve the general surgical care of children in Britain. Although all but one of the health regions has a specialist paediatric and neonatal surgical unit, most children are treated in district hospitals by general surgeons. Furthermore, although the number of consultant paediatric surgeons has recently increased, paediatric surgery has been classified as a shortage specialty. In the past, surgical trainees have been unwilling to contemplate a career in paediatric surgery because of the limited number of consultant posts, and they have, indeed, been actively discouraged from doing so by those already within the specialty. The signs are now that this restrictive attitude will change.

Despite present difficulties, Britain has led the way in paediatric surgery, and on p 1156 Jones describes some of what has been achieved as well as discussing what more might be done. The British Association of Paediatric Surgeons was founded in 1954 and was the first such association in the world. It continues to have a large international membership. One possible cause of the delay in expansion of the specialty in Britain has been the difficulty in defining the scope of paediatric surgery. Ear, nose, and throat surgery, orthopaedics, and neurosurgery were all established first as specialties, and plastic surgery emerged at about the same time as paediatric surgery—soon after the second world war. The work of paediatric surgeons varied depending on what other specialist surgeons were available, but the model of pioneers such as Denis Browne, whose repertoire covered the full range of children’s surgery, was unlikely to be appropriate for most.

The council of the British Association of Paediatric Surgeons...