Maintenance treatment with H₂ receptor antagonists in patients with peptic ulcer disease: rarely justified in terms of cost or patient benefit

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H₂ receptor antagonists have been successful in the short term management of peptic ulcer.^{1,2} In a lower dose taken at bedtime they also reduce the incidence of relapse of ulcers.³ Maintenance treatment with H₂ antagonists has been advocated for all patients with peptic ulcer⁴ but has been challenged by others.⁵ Here I question whether such maintenance treatment is routinely required. Firstly, consideration must be given to the natural course of the condition.

Natural course

Peptic ulcer is characterised by episodes of relapse and remission but may eventually remit totally in most patients.⁶ Treatment should alleviate symptoms, effect healing of the ulcer on relapse, and prevent haemorrhage or perforation. Although well recognised, complications are uncommon and are most likely to occur in patients with a previous complication.^{7,8} Most prospective trials of maintenance treatment have failed to show a significant reduction in rates of complication.⁹

Mortality in patients with peptic ulcer does not differ significantly from expected rates if patients at all stages of the condition are considered.¹⁰ Reports of increased mortality from peptic ulcer have focused on patients during relapse and those at risk of complications.^{11,12} The increased risk was only evident for two years, and the number of attributable deaths was small. Further evidence for the benign nature of peptic ulceration comes from a review of patients treated with placebo during clinical trials.¹³ Patients receiving placebo did not have a higher rate of complications from ulcers.

Efficacy of maintenance treatment

Maintenance treatment reduces the rate of symptomatic and asymptomatic relapse⁴ and keeps patients free of ulcers for longer than intermittent treatment.^{14,15} If patients receiving intermittent treatment develop a relapse their symptoms are quickly brought under control by a further course of medical treatment at full doses.⁵ Most patients find intermittent treatment acceptable.⁵

Might routine maintenance treatment reduce the risk of ulcer complications? If so, the argument that all patients should receive such treatment would be much stronger. It has, however, been difficult to show a reduced rate of complication when maintenance treatment was routinely given to patients with peptic ulcers.⁹ In a randomised study in general practice 219 patients whose ulcers healed when they took cimetidine were randomised to receive either maintenance cimetidine 400 mg at night or no other active treatment.¹⁶ The group receiving maintenance treatment had a reduced rate of symptomatic relapse. During follow up for two years, however, five out of 152 patients receiving maintenance treatment had episodes of bleeding compared with four out of 67 receiving no treatment ($\chi^2=0.304$; $p>0.5$). One patient receiving maintenance treatment suffered perforation and there were no deaths related to ulcer. Thus, although maintenance treatment reduced the rate of symptomatic relapse, it did not affect the rates of complication.

Financial implications of maintenance treatment

Peptic ulceration may affect 10% of the population at some time.¹⁷ Giving all patients maintenance treatment would impose an enormous financial burden on the NHS. Using 1986 prices, Venables calculated that it cost £4112 a year to treat 100 patients with duodenal ulcer with cimetidine intermittently (British Society of Gastroenterology and Smith, Kline and French international workshop, Welwyn Garden City, 1986). If these patients were all given maintenance treatment, and even taking into account the lower rate of relapse, the figure would be £11558. Thus routinely giving maintenance treatment might increase the cost of the medical treatment of duodenal ulcer almost threefold.

Safety of maintenance treatment

Cimetidine has been available in the United Kingdom since 1976, ranitidine since 1981. Both drugs have an excellent safety record to date. Their safety after being taken long term is, however, less certain. Some patients have received almost continuous treatment for nine to 12 years without apparent adverse effects.¹⁸ Indefinite maintenance treatment might be for much longer or conceivably for life,¹⁷ which may require close monitoring.

Targeting maintenance treatment to specific groups

Some groups of patients do require long term maintenance treatment. Mortality from peptic ulcer and rates of complications from ulcers have been rising in the elderly (see figures). This contrasts with a fall in the population as a whole since before cimetidine was introduced.^{19,20} Although maintenance has not apparently influenced the rate of complications in the general population,^{9,16} it is probably worth while attempting to keep ulcers healed in elderly patients. The elderly are more likely to have asymptomatic ulcers and to present with a complication. Most of the mortality from bleeding ulcers occurs in elderly patients.

The use of non-steroidal anti-inflammatory drugs has been linked to the increased incidence of ulcer

Death rates from gastric ulcer in England and Wales (open symbols) and in Scotland (closed symbols) for men and women aged 65 and over.²⁰ Reproduced with permission

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patients with healed gastric ulcers should be endoscopically re-examined every three months during the first year of maintenance treatment as the original healed gastric ulcer may have been malignant, and recurrence, which is usually fairly rapid, may be asymptomatic. Rapidly recurring gastric ulcers should therefore be treated surgically.

The duration of the relapsing tendency is not known, but in many or most patients with ulcer disease recurrences probably occur throughout life. Maintenance treatment must therefore also be life long, as with most other chronic diseases. Compliance with long term maintenance treatment is excellent because patients develop pain when treatment is stopped. The compliance can be reinforced by pointing out that "a tablet a day keeps the surgeon away."

Conclusions

Long term, and even life long, treatment with drugs is not objectionable provided that the treatment

is effective and safe. Maintenance treatment with currently available H₂ receptor antagonists is effective in keeping ulcers in remission and is safe because unwanted effects during maintenance treatment with these drugs have been so rare as to be truly remarkable.⁸

Maintenance treatment with H₂ receptor antagonists is, therefore, the current optimal treatment for patients with ulcer disease.

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Gastric ulcer perforation rates in England and Wales for men and women aged 65-74 and 75 and over.²⁰ Reproduced with permission

complications in elderly patients.^{19, 20} H₂ receptor antagonists are often prescribed to patients who are being treated with non-steroidal anti-inflammatory drugs, and they have been recommended routinely and for long term use in patients with a history of peptic ulcer who need to take non-steroidal anti-inflammatory drugs. H₂ receptor antagonists are effective in healing ulcers in patients being treated with such drugs,²¹ although their long term usefulness in maintaining healing has not been evaluated.²²⁻²⁴

Patients with a previous ulcer complication should be offered maintenance treatment as they are at a greater risk of further complications. Despite the lack of evidence that maintenance treatment with H₂ receptor antagonists reduces complications in general its selective use in patients with a more severe ulcer diathesis may be beneficial.

Patients with frequent episodes of relapse are also suitable for maintenance treatment. At the outset of the disease predicting which patients will relapse frequently is not possible, although certain risk factors, particularly cigarette smoking, may be identified.²² Bardhan has found that only 17% of patients will have three or more relapses a year.²⁵ Such patients may be quickly identified if treated intermittently and transferred to maintenance treatment. Currently most authorities agree that universal maintenance treatment after the first attack of duodenal ulcer entails treating many patients unnecessarily.^{5, 16, 17, 25}

Summary

Maintenance treatment reduces the frequency of

ulcer relapse. Its routine use is unnecessary because the condition is benign and most patients do not relapse frequently. Routine maintenance treatment does not reduce the incidence of complications of ulcers overall, although it may do so in specific groups mentioned above. Routine maintenance treatment for all patients with ulcers would be expensive as well as largely unnecessary.

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