Ranitidine in the Management of Acute Duodenal Ulcer

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Abstract
The H2-receptor antagonists have had a major impact on the management of ulcer disease, allowing us to achieve a degree of symptom relief and a level of ulcer healing which has not been possible before. Studies with ranitidine have shown that a single night time regimen or, if preferred, a divided 150 mg BID dosage, will achieve healing in three quarters of ulcers after 4 weeks and 95% after 8 weeks. It is a convenient and safe treatment.

Introduction
While many factors are involved in the development of an ulcer, the concept of an imbalance between mucosal defences and acid peptic attack is an important one. In the case of duodenal ulcer (DU) particularly, it seems as though acid plays a crucial role. Therefore drugs which either neutralise or suppress acid are used in its treatment. The development of H2-receptor antagonists (H2-RA), cimetidine and, more recently, ranitidine, has provided most valuable treatments for ulcer disease as they are convenient, effective and safe.

Preliminary Results
Early studies of ranitidine against placebo have been reviewed by Colin-Jones and Dobrilla. The most commonly used dose was 150 mg twice daily and in every trial there was a statistical significance in favour of ranitidine.

The next crucial test was to compare ranitidine with cimetidine. Initially cimetidine was launched with a dose schedule of 200 mg three times daily with meals, and 400 mg at night. Numerous trials have compared ranitidine 150 mg BID with cimetidine, usually in that original dose regimen, but sometimes with 400 mg BID which is now more commonly used. The effectiveness of 4 weeks' treatment seemed to be similar: there was an 6% advantage in favour of ranitidine (74% versus 68% healing) from the cumulative data on over 1300 patients treated with either ranitidine 150 mg BID or cimetidine 1 g/day. Ranitidine was well tolerated and caused no serious adverse events.

Night Time Treatment
Night time acid secretion has been known to be important in duodenal ulcer disease since 1932, but it was Dragstedt in 1962, in his early work on vagotomy, who demonstrated that acid secretion is much higher in the duodenal ulcer population compared with the control and that this difference in acid secretion was more marked during the night than it was during the day. This has been followed up recently by Gledhill et al. who, using both cimetidine and ranitidine, demonstrated that doubling the night time dose increased the degree of night time acid suppression. By giving ranitidine 300 mg in a single night time dose instead of a divided dose of 150 mg BID, the overall 24-hour reduction of acid output remained virtually the same (62% versus 63%) but the overnight secretion could be reduced by 85% compared with 56%. The daytime reduction of acid in the absence of morning dose was correspondingly less. The striking reduction in the overnight acid secretion with ranitidine 300 mg given before retiring to bed prompted Ireland et al. to undertake a randomised double blind trial in which 102 patients were treated with ranitidine either as a divided regimen of 150 mg BID or as 300 mg nocte. The respective healing rates at 4 weeks were similar (84% and 96%). Of some interest was the finding that the usual adverse effect of smoking on ulcer healing rate, which was observed in the divided dose group, was not observed in the 300 mg nocte group. Disappointingly this finding has not been confirmed in other trials. Both treatments were well tolerated, and there was no difference in relief of symptoms or in the incidence of adverse effects. One patient developed a possible hepatitic reaction to ranitidine, which resolved completely.

Subsequently two further multicentre studies have been carried out, in the UK and Ireland and in Continental Europe, comparing ranitidine 150 mg twice daily with 300 mg at night. Lee et al. entered 594 patients in a randomised controlled trial with strict criteria for timing of endoscopy and patient compliance. Because of the strict criteria only 424 patients were found suitable for analysis. Relief of symptoms was similar in the two groups. Healing rates were also similar: 83% and 78% at 4 weeks, which increased to 97% after 8 weeks.
of treatment. There was no benefit for the smokers in the 300 mg night time group. Both treatment regimens were well tolerated and no serious adverse events occurred.

The third trial, using the same protocol as that of Lee et al., involved 77 centres in 9 European countries. Of 864 patients with active duodenal ulcers entered into the study, using the same strict criteria, 605 were found suitable for analysis. Good relief of symptoms was achieved in both groups and the healing rates were almost identical: 82% and 76% at 4 weeks, which rose to 95% and 94% after 8 weeks of treatment. Adverse events were again infrequent and the treatments were well tolerated.

These trials show clearly that 300 mg of ranitidine given at night is just as effective as the divided dose of 150 mg BID and continuing treatment for 2 months leaves only about 5% of ulcers unhealed.

The Resistant Ulcer

It can be seen that the prolonged use of an \( H_2 \)-receptor antagonist will lead to healing of almost all ulcers. Prolonging treatment for a period of 2 to 3 months will increase the healing rate. There still remains a small group of resistant ulcers. These patients do not seem to suppress their acid overnight with either cimetidine or ranitidine. The explanation for this is not known. The ulcer which is resistant to one \( H_2 \)-receptor antagonist probably does not heal more effectively by changing to the other. Treatment options for such patients include changing the medication to a bismuth-containing preparation such as colloidal bismuth or possibly adding pirenzepine to the \( H_2 \)-receptor antagonist regime to achieve potentiation of acid and pepsin suppression. It must be stressed that patients whose duodenal ulcers do not heal with an \( H_2 \)-RA form a small group who may require surgery.

Ulcer Recurrence

The biggest problem with ulcers is not accomplishing healing but preventing recurrence. There are a number of adverse prognostic features like prolonged pain in the last attack, smoking, high peak acid output, stenosis of the duodenal bulb, young age of onset of ulcer symptoms, positive family history and persistent duodenitis after ulcer has healed. Probably the most important of these is smoking. The response of the duodenal ulcer to the \( H_2 \)-RA appears to be diminished by smoking and the relapse rate is more frequent. Patients must therefore be advised to stop smoking. The other factor is the severity of the ulcer disease.
namely severe scarring or a deep ulcer and persisting inflammation after the ulcer has healed.1,2

The patient with a good prognosis will typically be a patient with a series of short attacks of pain, occurring not more than 2 or 3 times a year, with the symptoms not severe enough to stop him from working, who is a non-smoker and who has no severe scarring or deep crater on endoscopy.

Individual Management

The decision whether to use a divided dose of an H2 antagonist or a single dose, such as ranitidine 300 mg at night, is a matter of personal choice and convenience. The single night time dose should improve patient compliance while leaving the daytime gastric secretion unchanged. There has been considerable controversy over the theoretical risks of too great a reduction of gastric acid,3 therefore the suppression of acid just at night has attractions. The guidelines described earlier give some indication as to how a particular patient is likely to fare. The patient with a good prognosis needs only intermittent courses of treatment as soon as his ulcer symptoms recur. Further investigation each time the ulcer relapses is not required, provided that the patient recognizes the symptoms as being identical to the previous episodes. The patient with poor prognostic features needs a prolonged course of healing treatment, perhaps extending for 2 months. Such a patient will usually require maintenance therapy. How long this should be continued is uncertain, but data from a trial involving the prolonged use of cimetidine over 3 years suggest that after 2 years those whose ulcers have not relapsed whilst on maintenance therapy have a better than average prognosis.4 It would seem reasonable therefore to give a 2-year course of maintenance therapy which should then be stopped and the cycle repeated should the ulcer recur. On the other hand if the patient has had a complication, or is elderly, or has another disease, then the risk of a further complication in that patient is greater than average and, especially in view of other disease, lifelong therapy should be undertaken.

The Table gives the suggested management of a patient with duodenal ulcer.

References


