Editors:
A. Torsoli
P.E. Lucchelli
R.W. Brimblecombe

Further Experience with

H_2-RECEPTOR ANTAGONISTS

in Peptic Ulcer Disease and
Progress in Histamine Research

European Symposium
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Foreword

The developments that have led to the discovery of the H_2-receptor antagonists have been a long succession of hopes and disappointments. As was recalled in a recent article*, many problems, not only of a scientific but also of a social nature, had to be tackled and solved. Now, however, we have at our disposal a drug, cimetidine, which is capable of dramatically changing the concept of treatment in one area of human pathology, and we owe it not to good luck but to the logical elaboration of ideas and to the joint efforts of chemists and biologists.

The introduction of cimetidine has changed the quality of life of many patients, and it has had important socioeconomic effects. Of even greater importance, it has prompted reconsideration of a number of chapters on physiology and clinical medicine. Many owe much to the few who from 1964 on have planned and guided a program that promises so much. At that time, none of them would have believed that it would take so long.

The European Symposium at Capri, the proceedings of which are published in the present volume, constitutes a further proof of the twofold value of cimetidine: on the one hand as a drug for the treatment of peptic ulcer and related conditions, on the other as a tool for the study of the normal and pathological physiology of histamine. In the pages that follow, the latest results are reported of controlled clinical studies in various areas of esophageal, gastric and duodenal pathology, data are presented on the side effects and the safety of the drug, and the results and prospects are described of studies of the histamine receptors in the digestive tract and other systems.

The combined contributions of scientists belonging to different disciplines and from many countries testify in their turn to the value and the efficiency of interdisciplinary and international cooperation.

Aldo Torsoli

*Duncan, W.A.M. and Parsons, M.E. (1980): Reminiscences of the development of cimetidine. *Gastroenterology 78,* 620-625.

Changes and perspectives in the management of peptic ulcer disease since the introduction of H_2-receptor antagonists

Chairmen: J.H. Baron *(London, United Kingdom)*
L. Barbara *(Bologna, Italy)*

Cimetidine in duodenal ulcer: the present position

K.D. Bardhan
District General Hospital, Rotherham, United Kingdom

Introduction

It is only 4 years since cimetidine became generally available, yet during this time it has radically transformed the treatment of duodenal ulcer and added greatly to our knowledge. The purpose of this paper is to provide a summary of the results achieved with cimetidine so far and to point to some directions for future research.

Past problems with medical treatment

In the past, the value of medical treatments for ulcer disease was uncertain, for 4 main reasons.

First, the cause of ulcer disease was unknown. Indeed, there are likely to be several different causes, the relative importance of which varies from patient to patient. Consequently, there was no firm rational basis for treatment.

Second, the disease is benign and runs a spontaneously relapsing and remitting course. Therefore, the value of a medical treatment can only be judged in double-blind clinical trials. Though such trials are now commonplace, it is often forgotten that they are a fairly new development. Some trials are still defective; in particular, the number of patients studied is frequently small. In a disease like duodenal ulcer, where about one-third of patients heal spontaneously in a short period, to show that a given treatment doubles the healing rate, approximately 80 patients are required in the study, half treated with placebo and the other half with the compound under investigation. Even then, there is a 20% chance that the benefit of the treatment may not be seen in the population of patients studied (the 'rogue' population). To reduce this chance to a more acceptable 5%, the sample size would need to be 140 patients. Very few studies, even with cimetidine, are of this size [1].

Third, there is often a lack of correlation between ulceration and symptoms. Ulcers are often asymptomatic when they recur; by the time symptoms develop, the ulcer has been present for weeks or even months [Bardhan, unpublished observations]. In other patients, ulcers cause troublesome symptoms but some relapses are virtually silent. Also, symptoms often disappear before healing is complete. Finally, there is no relation between the number or size of ulcers and the severity of symptoms. Therefore, relief of symptoms alone cannot be taken as a measure of ulcer healing.

Fourth, to determine whether a treatment influences duodenal ulcer healing, objective evidence is required. This is possible only by using fibreoptic endoscopy; double-contrast barium meal X-ray examinations, though accurate for making a diagnosis of duodenal ulcer, are not sensitive enough to follow its healing. Forward-

viewing endoscopes allowing a proper yet easy examination of the duodenum became widely used in Britain only in the early and mid 1970's; indeed, the first study on duodenal ulcer healing using endoscopic assessment was published only in 1972 [2]. Therefore, the conclusions of earlier studies on duodenal ulcer healing, before endoscopy became available, may not be accurate. It is ironical that, had cimetidine been discovered in the 1960's, before the wider use of endoscopy, it would have been difficult to confirm its ulcer healing effect.

The significance of acid

Though the cause(s) of ulcer remain unknown, it has been recognised for many years that the presence of acid is essential for the development of ulcer. It is presumed that mucosal integrity is maintained by a balance between 'attacking factors' consisting of acid and possibly pepsin and bile, and 'defence factors' which presumably lie in the innate nature of the mucosa itself, and mucus. When the balance is tilted in favour of the attacking factors, ulceration results; when the balance re-establishes itself, healing follows. Little is known of the nature or mechanism of mucosal defence; rather more is known about acid. Therefore, not surprisingly, the main direction of anti-ulcer treatment has been to try and reduce acid.

Medical treatment before cimetidine

Medical treatment before the introduction of cimetidine consisted of antacids, anticholinergics, rest, diet and sedation, given singly or in combination.

Antacids do reduce acid, but only when given in large amounts. However, it has been wrongly assumed that antacids have little effect on ulcer healing [3, 4] and, therefore, they have traditionally been used in small amounts, and only to relieve symptoms. Anticholinergics reduce acid secretion, but their use is limited by side-effects [5]; there is no firm evidence that these compounds increase ulcer healing, though they may reduce recurrence when treatment is continued [6]. Bed rest has long been known to relieve symptoms, and recent evidence from cimetidine trials, albeit indirect, suggests that it increases ulcer healing as well [7]; though effective, taking time off work can be expensive for the patient. Restricted diets and milk-based diets have commonly been used in the mistaken belief that they buffer acid more effectively than ordinary food; in fact, the effect is similar [8]. Such diets may help in relieving symptoms, but there is no evidence that they increase ulcer healing. They also have the disadvantage of placing a burden on the domestic arrangements of patients. Sedation has been frequently recommended, but its value has not been proven.

A different approach was to use carbenoxolone, to increase mucosal defence; the first time this agent was studied, however, it was not found to be effective [2]. Colloidal bismuth in the form of tricitrato-dipotassium-bismuthate supposedly acts by providing a protective coating for the ulcer; in studies using endoscopic assessment, it was shown to increase ulcer healing [9].

The effect of cimetidine on acid secretion

It was against this background of largely ineffective ulcer treatment and the failure

to reduce acid secretion effectively by medical means that the development of the histamine H_2-receptor antagonist cimetidine took place; the story of this development has been recounted elsewhere [10-12].

The most striking effect of cimetidine is reduction in gastric acid secretion. Basal and nocturnal secretion are profoundly reduced and maximal secretion, evoked either by food or by pharmacological stimuli, is greatly lessened. Over 24 hours, acid secretion is reduced by about two-thirds [13, 14]. Thus, for the first time, it became possible to achieve acid inhibition by a drug, of an order produced by vagotomy. The dose of cimetidine required for this was 1 g/day, administered in 3 daily doses of 200 mg and 400 mg at bedtime.

The effect of cimetidine on ulcer healing

Having determined that cimetidine reduced acid secretion, the next step was to investigate if it healed duodenal ulcer. This was done in numerous short-term studies conducted in many parts of the world; the trials were organised by Smith Kline & French and had a similar design (for a review of these trials, see [7]).

Patients with duodenal ulcer proven by endoscopy were randomly assigned to treatment with either cimetidine or placebo. The dose of cimetidine varied from 800 mg to 2 g daily, but the doses most commonly used were 1 g and 1.2 g daily. The duration of treatment varied from 2 to 12 weeks, but was generally 4-6 weeks. At the end of this period, endoscopy was repeated. The results were judged by 2 principal criteria: first, by comparing the proportions of patients in the 2 treatment groups whose ulcers had healed; second, by comparing the degree of symptomatic improvement.

The results of trials in Britain were similar. In 4-6 weeks, about 30% of patients on placebo healed spontaneously, compared with 60-80% of those on cimetidine. The relief of symptoms was dramatic, the majority of cimetidine-treated patients becoming pain-free or nearly so within a week. Similar results were obtained in the trials conducted in Italy, Sweden, Denmark and Australia.

Virtually all of the studies confirmed that cimetidine accelerates ulcer healing; the exceptions were the trials conducted in Norway [11], Switzerland [15] and the United States of America [16]. In these studies, though cimetidine produced a higher healing rate, the placebo healing rate was so high that the difference was not statistically significant. The study from the U.S.A. was the largest single trial; the high placebo healing rate may have been due to the large amounts of antacids taken by patients in this group, which is known to increase ulcer healing [17].

Pooling the results of the different trials, the main finding is that, in 4-6 weeks, approximately 40% of out-patients will heal spontaneously, whereas with cimetidine the figure rises to about 75% and symptomatic relief is much more rapid.

Failure to heal rapidly

The majority of patients heal rapidly; what happens to the remainder? There is much speculation as to whether such patients form a distinct subgroup of duodenal ulcer disease.

Some investigators present at the Capri symposium mentioned that their patients did not heal with continued cimetidine treatment, i.e., they had a resistant ulcer. My experience has been different: with continued treatment, the majority of patients

heal, about 70% in 1 month, about 80% in 2 months, about 90% in 3 months, and 95% or more in 4 months. These differences in results are not readily explained, but may have something to do with studying different populations of patients.

Some patients are undoubtedly 'slow-healers' and take several months to heal with each course of cimetidine; however, this is only a very small group. In other patients, successive recurrences take progressively longer amounts of time to heal with cimetidine, giving the impression that the patient is becoming resistant to the drug; however, the reverse is also true. In the majority, 'slow-healing' is simply a matter of definition; those that have not healed fully in a few weeks have nevertheless either partially or almost completely healed, and are generally asymptomatic. If healing is nearly complete and cimetidine is stopped, healing generally goes on; cimetidine has helped to restore the balance between attack and defence, which is then sustained.

Non-compliance is another reason for slow healing; patients taking cimetidine soon become asymptomatic, and the urge to continue treatment then lessens. However, it is difficult to be certain how important a role this plays.

Patients with Zollinger-Ellison syndrome may present with a resistant ulcer though, in many, the standard dose of cimetidine produces healing [18]. Hypercalcaemia due to hyperparathyroidism has also been reported to cause apparent resistance to treatment [19]. Both conditions are very rare and there is little to be gained in the routine measurement of acid secretion and blood gastrin levels. In my experience, patients with slow healing have normal gastrin levels and a wide range of acid and pepsin secretion similar to those who heal more quickly.

Management after the ulcer has healed

While the value of short-term treatment of duodenal ulcer with cimetidine is no longer in doubt, further management is controversial since, when the drug is stopped, the patient is prone to relapse. There are 3 options available: first, further treatment for a fixed duration, second, long-term maintenance treatment, and third, intermittent treatment.

Further treatment for a fixed duration

The basis for this option is that, though short-term treatment does not influence the natural history of the disease, a longer period of treatment may do so.

In various studies, patients whose ulcers had healed following treatment with cimetidine were kept on the drug for periods of up to a year, with doses of up to 1 g/day. While on treatment, the relapse rate was low, but after the drug was withdrawn there was a high rate of relapse, similar to that in patients who had received only a short course of treatment [20-24].

In a large study which is still continuing, patients with duodenal ulcer who had healed within 1 month of beginning cimetidine treatment were randomly allocated to further treatment either with placebo, or with cimetidine for either 2 or 5 months, followed by placebo [25]. Endoscopy was carried out every 3 months in asymptomatic patients, and earlier if symptoms developed. Preliminary results show that the proportion of patients who relapsed on placebo was similar in all 3 groups: during the first 22 months of follow-up, 55-60% had a symptomatic relapse, and 70-77% had a silent recurrence; the rate of relapse in the different groups was also similar.

Thus, there is generally no advantage to extending treatment for a fixed duration, as this does not influence the subsequent relapse rate. The exceptions are: first, to keep a patient in remission until definitive ulcer surgery, and second, and this is much less certain, to tide a patient over a stressful period (for example, when undergoing surgery on some other part of the body, or if ill for another reason, since an ulcer relapse at this time could be particularly troublesome).

Long-term maintenance treatment

This has been investigated in several studies, and all confirm that maintenance treatment markedly reduces the relapse rate (for review, see [7]). In these trials, patients whose duodenal ulcer had just healed in short-term studies were randomly allocated to further treatment with either placebo or cimetidine. The dose of cimetidine varied from 400 mg nightly to 400 mg both at night and in the morning; the duration of treatment was generally 6-12 months. Patients were seen frequently; if symptoms recurred, endoscopy was carried out, but if not, only a final check gastroscopy was done at the end of the study. The 2 criteria used to judge the results were: comparing the proportion of patients in the 2 groups whose ulcers recurred with symptoms, and comparing the proportion of patients with an asymptomatic ('silent') relapse.

The trials were organised by Smith Kline & French and were of similar design. The results of the various studies when taken together show that, amongst those on placebo, 47% had a symptomatic relapse within 1 year, compared with only 13.4% of those on cimetidine 400 mg nightly and 13% of those on cimetidine 400 mg twice daily. The corresponding figures for silent ulceration were 30%, 5.3% and 9.3% [26].

These differences are remarkable and clearly indicate the value of maintenance treatment as a prophylaxis against ulcer recurrence. Nevertheless, there are several problems which need investigation.

First, will maintenance treatment remain effective? Approximately 1 out of 7 patients on cimetidine relapse in the first year. Will similar proportions relapse in subsequent years? In 1 study where patients were maintained on cimetidine 1 g/day for up to a year, the relapse rate steadily increased with the passage of time [20]. If this is confirmed, then maintenance treatment is merely delaying the relapse rather than abolishing it. Alternatively, will the majority of those who relapse on maintenance treatment do so in the early period? If so, such patients could then be selected for surgery. Unfortunately, no data exists on the results of treatment for longer than a year.

Second, for how long should treatment be continued? The tendency to relapse can last a life-time; therefore, maintenance treatment may need to be permanent. However, the majority of patients run a more limited course: symptoms steadily increase, reaching a peak 5 to 10 years after the onset; thereafter, there is a strong tendency for remission [26, 27]. Therefore, treatment is required for a shorter period, only for as long as relapse is likely. The problem is that there is no method by which the natural history of the disease can be predicted in individual patients.

Third, does maintenance treatment cure duodenal ulcer disease or merely suppress it? On the evidence so far, it merely suppresses. However, with prolonged treatment, the natural history of the disease may be altered.

Fourth, what is the optimal dose? Maintenance with 400 mg nightly fails to prevent all relapses. Surprisingly, the 800 mg dose is no more effective. Will a higher

dose produce better results? And also, will combination with other drugs improve results?

Fifth, do all patients need maintenance treatment? Clinical experience shows that many patients have only occasional attacks; such patients probably do not require prolonged treatment. How should candidates for maintenance treatment be selected at the outset?

Sixth, cimetidine has so far been very safe. But will it remain so with very long-term treatment?

These questions will take many years to answer.

Intermittent treatment

Intermittent treatment, given as and when symptoms recur, is commonly used in practice, but its value has not been formerly investigated. I studied this method in 125 patients who were treated with cimetidine until healing was complete, which generally took 1-2 months. Thereafter, their progress was followed for up to 22 months. During this time, 83 patients relapsed and, of these, 21 defaulted. The remaining 62 patients were re-treated until healed, but 36 later relapsed again.

The pattern of relapse and remission for the group as a whole was similar on both occasions, confirming that a short course of treatment does not alter the natural history of the disease. The likelihood of relapsing was 9% at 1 month or less, 23% at 3 months or less, and 40% at 6 months or less. Conversely, 60% were likely to be in remission at 6 months, 48% at 9 months, and 38% at 12 months. But in individual patients, there was little correlation between remission periods. Some who relapsed within 1-2 months after 1 course of cimetidine relapsed after 12 months or more following the second course; the reverse was equally true.

Amongst patients I see, the majority have 1, 2 or sometimes 3 significant attacks a year. In most, symptoms develop only gradually and there is therefore enough time to intervene with a short course of cimetidine, which terminates the attack, provides rapid relief and produces quick healing. However, not everyone is suited for such treatment. Those who in the past have bled or perforated without warning, or who usually develop severe symptoms abruptly, should not be treated in this manner as there is not sufficient time to intervene. Intermittent treatment is also best avoided in the elderly or those with severe associated disease, such as cardio-respiratory problems, for there is a small but unavoidable risk of bleeding or perforation with each ulcer recurrence, which in this group could have serious consequences. Overall, about one-fifth of patients are not suited for such treatment.

Despite these limitations, intermittent treatment is simple, is cheaper than maintenance treatment as less drug is used, and allows detection of 'rapid relapsers' who can then with confidence be selected either for maintenance treatment or for surgery [29].

The severity of ulcer disease and the method of and criteria for referral to specialist units varies from place to place. Therefore, the results of intermittent treatment may also vary from centre to centre. Thus, in one study, continuous treatment was preferred to intermittent treatment [30]; in my practice, on the other hand, intermittent treatment provides an adequate alternative to maintenance treatment for the majority of patients.