SOME ASPECTS OF THE MEDICAL MANAGEMENT OF PEPTIC ULCERATION*

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In the management of peptic ulceration questions of environment, occupation, diet, habit, working hours, systemic infections and emotional stresses are some of the factors that have to be considered. We have tended to think of these matters largely in terms of how they affect gastric acid secretion, but we must regard the problem of ulcer causation as multifactorial and not just as concerning acid and pepsin secretion alone.

Vagal stimulation and antral distension, by their action on the secretion of gastrin, are of course the two main ways in which gastric acid excretion is excited, so that vagotomy and antrectomy are naturally two ways in which this secretion may be arrested therapeutically. The synthesis of two gastrins from the antral mucosa of the dog by Gregory and Tracey[10] in 1964 was a major advance in gastro-enterology, and if it were possible to neutralize gastrin itself as it is being secreted, this should produce the same result as surgical arrest. Such an approach as this, though perhaps not a radical removal of the cause of ulceration, would nevertheless be an advance in the control of ulcers and possibly in the prevention of their recurrence. We are now able to break up at least one gastrin from its 17-amino-acid molecule into active fragments, so that changes in the structure of such fragments might produce a substance antagonistic to the hormonal action of the whole gastrin. Already one such compound has been prepared in the laboratory and shown to be a powerful inhibitor of gastrin. The synthesis of analogues of this compound is being studied and if their side-effects in human beings can be shown not to be too great, there is clearly a hopeful prospect of a new and valuable therapeutic agent.

Apart from the question of acid control and the general problems of regimen and management, most of us have come to rely, in the treatment of the active phase of peptic ulcers, upon bed rest, avoidance of smoking, dietary control, alkalis and perhaps sedative or anticholinergic drugs. In dieting it is doubtful how far irregular meals or dietary indiscretions are often of primary aetiological importance, and it is certainly not just a question of eating only the best sorts of food to buffer acid. Indeed, the greater the buffering action of a food, the better it may act as a stimulator of acid as, for instance, with protein foods which are good buffers but excellent acid provokers (Williams *et al.*).[27]

A considerable part of the general management of the ulcer patient lies in the discussion and explanation given him by his physician, and this part of the treatment must be given proper time and care. Rest must not be thought of in terms of a simple holiday away but as a readjustment of outlook which may involve changes in emphasis both in professional and personal life. It is in this respect that the good gastro-enterologist can be of most help if he is able to keep a patient at work while at the same time moderating his reactions to responsibilities and anxiety.

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Over many years many forms of drug treatment have been recommended, but the unpredictable behaviour of ulcers, with their tendency to remit spontaneously and to react to psychological factors, makes it extremely difficult to assess accurately the part played by a single drug in treatment.

In Great Britain a new preparation, carbenoxolone sodium—a triterpenoid prepared from glycyrrhetinic acid—has already become part of the standard medical management for the treatment of gastric ulcer. There have been many reports on the results of its use, most of which have been assessed by measurement of the ulcer crater on X-ray films, and it is now generally accepted that, in the recommended dosage, ulcer healing can be accelerated by carbenoxolone.[1,2,7,8,12] It has the advantage that patients can remain at work while taking the drug and no strict dieting is necessary. Many benign gastric ulcers will heal spontaneously or on a placebo, and surgery offers a satisfactory—though not wholly perfect—answer if it becomes necessary. Nevertheless, I believe that this new drug, carbenoxolone, represents an important advance if for no other reason than that it appears to produce its effect through its action upon mucus secretion and the protection this affords against acid peptic digestion of the mucosa.

During the last 2 years there have been clinical reports on its use in the treatment of duodenal ulcer,[17] and at a symposium on carbenoxolone sodium held in London in 1967 four clinical trials were reported.[4,5,13,20] With others[6] I have previously reported a clinical trial with Duogastrone (carbenoxolone capsule) in duodenal ulcer, which was concerned only with the short-term results as assessed after one month's treatment.

In carrying out this type of trial it is necessary to select those patients who present with symptoms and in whom a firm diagnosis can be made from clinical and radiological evidence. It is not necessary to demonstrate an actual ulcer crater if the history is characteristic and if an abnormal duodenal cap is found on X-ray. If these criteria are accepted, a properly conducted blind trial using a placebo should be able to show whether the results on duodenal ulcers are similar to those obtained in the more easily assessable gastric ulcers.

MATERIALS AND METHODS

Duogastrone capsules or placebo capsules which were indistinguishable from those containing the drug were given 4 times a day before meals, and the code was kept by the dispenser so that neither patient nor doctor knew which was being given. Patients were numbered sequentially.

Clinical assessment of the patient's pain was graded as follows:

1. Moderate pain relieved by food or alkalis, not waking at night.
2. Severe pain relieved by food or alkalis and waking at night.

3. Not relieved by food or alkalis, waking at night, and radiating to the back.

The patient's nervous stability (also graded into 3 groups), smoking habits, any previous ulcer complications, family history, and working hours lost during the 12 months before the trial were recorded. General examination included a record of blood pressure readings, weight, and any abnormal side-effects, particularly oedema; in most cases the serum electrolytes were estimated and electrocardiography was carried out. If any additional treatment was given this was noted.

Barium-meal examination was carried out in all cases, and in this trial only those in which an ulcer crater was reported were included.

It became clear early in the trial, however, that attempts to measure a duodenal ulcer crater and assess its changing size under treatment were either inaccurate or impossible. It is, in fact, only possible to judge by the patient's symptoms, and since these cannot be measured objectively this must introduce some observer and patient error. In a double-blind trial this should not seriously influence the findings, but in a straight trial or treatment it is important to make some attempt at a constant grading, and to have enough cases to minimize the observer error.

During the trial patients were each given a typed card with instructions to take the capsule 15 - 30 min. before meals 4 times a day, to eat their normal diet (only avoiding foods which they knew gave them symptoms), and to take alkalis only if they needed to do so for relief of pain. No other treatment (and in particular no anticholinergic drugs) was given. Patients were seen after 2 weeks' and after 4 weeks' treatment, and repeat barium meals were carried out at the end of the 4 weeks.

RESULTS

The results at the end of 4 weeks' treatment (Table I) showed a statistically significant difference ($P<0.001$) between the patients on Duogastrone therapy and those on the placebo. Patients on Duogastrone attained considerably better symptomatic relief than the controls.

TABLE I. RESULTS AFTER 4 WEEKS

Preparation	*No. of patients*	*Complete relief**	*Some improvement*	*No improvement*
Placebo	19	4	9	6
Duogastrone	15	13	1	1
Total	34	17	10	7

*Patients who had no symptoms and in whom no visible ulcer crater was found at repeat X-ray examination.

All the patients were ambulant during the trial and no significant side-effects were noted.

DISCUSSION

Clinical assessment requires large numbers of patients, and should, if possible, be continued over a long period. To observe symptomatic response to treatment for 1 - 3 months can give an opinion as to the healing of the active ulcer but of course no ideas as to long-term 'cure'. Nevertheless, it is important to know if a new drug can improve the rate of healing—as judged by relief of symptoms—which can usually be expected either by standard orthodox treatment, or spontaneously. From the very large numbers of past reports published on the treatment of duodenal ulcers, it is probably fair to assess the average 'immediate relief' of symptoms from various previously tried methods of medical treatment to be about 55%; the average permanent relief—without recurrence—being probably not greater than 30%.

In the trial reported above I was struck by the way in which many Duogastrone patients ceased needing alkalis within 2 or 3 days of starting treatment. However, there is some uncertainty as to the extent to which the habit of taking alkalis may be kept up by the patient as a form of insurance even in the absence of pain. All the trials so far published have been concerned with short-term results, and no figures have been published for treatment by Duogastrone for periods longer than about 1 year.

The success of carbenoxolone in healing gastric ulcers depends essentially upon the local action of the drug in the stomach itself, before its absorption into the blood stream. Similarly, in the treatment of duodenal ulcer, success must depend upon getting the drug into contact with the ulcer, even if only for a relatively short time. It is possible that since carbenoxolone is largely excreted as unchanged conjugates in the bile, it might exert some effect in this way, but, if so, it can only be present in extremely dilute solution. Capper[3] suggested that its beneficial action on gastric ulcers might be due to the carbenoxolone in the bile reducing or antagonizing the irritant effect of the bile coming into contact with acid after regurgitation into the stomach, but this does not seem very probable. Biliary reflux is, however, an important factor in the causation of gastric ulcers, the patency of the pylorus (upon which regurgitation depends) varying with the pH on the duodenal side and also with the purely mechanical question of posture. Thus, although bed rest is a time-honoured means of helping an ulcer to heal, exactly how this comes about is not easy to understand. Posture may be one factor concerned, since lying supine in bed as compared with being in the upright position may be beneficial by affecting the way in which bile regurgitates through the pylorus. Bile salts in contact with the antral mucosa act as potent gastric irritants, and in the supine position there is less biliary reflux into the stomach than in the upright position. In this way bed rest could result in less gastric stimulation and less damage to the gastric mucosa by the bile salts themselves. Rhodes *et al.*[24] have shown that patients with active gastric ulcers have a greater reflux of bile salts into the stomach than normal, though this seems to revert to normal after the ulcer heals.

The fundamental problem in using carbenoxolone for duodenal ulcers lies in getting the drug undiluted into contact with the duodenal mucosa. Prolonged efforts have been made to produce an ideal capsule which will prevent the drug from being absorbed in the stomach and will deliver its contents unchanged into the duodenum, and work is still going on to devise the perfect method of administration.

Intensive study of various formulae for so hardening a gelatine capsule that it would rupture near or in the pylorus at about the right time in digestion led finally to the present Duogastrone capsule. This capsule contains

50 mg. of the drug combined with 900 mg. of sugar and small amounts of tartaric acid and sodium bicarbonate, and is administered 15 - 30 min. before food 4 times a day.

In most cases (but probably not all) it slowly swells during 30 - 90 min. in the gastric juice and reaches the pylorus where the contractions of the antrum cause it to rupture and discharge its contents.

By X-ray examinations with barium-filled capsules and other methods, success has been achieved in from 75% to 90% of capsules, though results are not yet 100% consistent. Craig *et al.*[9] found that the capsules ruptured at the pylorus in approximately 75% of cases; and Parke and Lindup,[23] using ^{14}C-labelled carbenoxolone (50 mg.) together with barium sulphate (210 mg.) in the Duogastrone capsules, found that 3 out of 4 capsules burst at $1\frac{1}{2}$ - $2\frac{1}{2}$ hours after swallowing. They noted that the maximum blood levels of Duogastrone in these cases occurred at 3 - 5 hours after administration as compared with the maximum at 1 - 2 hours when plain Biogastrone was given and absorbed in the stomach.

Taken shortly before food, the Duogastrone capsule will float on the upper layer of the stomach content (in the erect position) and remain there long enough to absorb fluid, being later carried to the pylorus, which will normally close against it. It is then milked to and fro in the antral region for a time until it has swollen and softened sufficiently (usually in about an hour) to be burst by the pyloric contractions, after which its contents are discharged into the duodenum. Here it is in contact for only a short time with the mucosa and the ulcer, but long enough to fix the protein of the mucus onto the surface cells of the ulcer. The distension of the capsule is produced by the formation of carbon dioxide after water absorption and is maintained by the sugar through osmosis.

Side-Effects

Carbenoxolone sodium is a highly active drug, and has some steroid-like effects. After absorption from the stomach it reaches a high level in the blood (60 - 80% of the dose) and is excreted as a glycuronide conjugate mainly in the bile; a part then undergoes further absorption giving an entero-hepatic circulation. In high dosage it may cause sodium retention, potassium loss and a rise in blood pressure. When Biogastrin is given, the risk of side-effects is clearly greater than when the Duogastrone capsule is given, since with this there should be no gastric absorption, absorption from the intestine being much slower than from the stomach and not producing any secondary rise in blood level or entero-hepatic recirculation.

The risk of side-effects is greater in patients who have any degree of cardiac failure (owing to possible sodium retention and oedema), renal disease, or in general in patients over 65 years who have arteriosclerotic changes.

Using Biogastrone, the incidence of oedema can usually be easily controlled by the simultaneous administration of a thiazide diuretic. Doll *et al.*[9] have shown that though there are fewer side-effects, the rate of healing of gastric ulcers is slowed if the dose of carbenoxolone is reduced from 300 mg. to 150 mg. daily.

Hydrochlorthiazide does not impair the healing effect; but spironolactone seems to block this, although fully controlling side-effects.

In many blind trials it is interesting to note that toxic effects from placebos often have the same incidence as from the active drug. This has proved true with Duogastrone.

There is evidence that, like spironolactone, the simultaneous administration of anticholinergic drugs may slow down the healing effect of carbenoxolone and perhaps also aggravate any side-effects.

Mode of Action

The concept of a mucous barrier of the stomach and duodenum is, of course, not new—Hollander[11] discussed it fully in 1954—but how it may act and how it may be influenced by drugs still needs more investigation.

Mucin is a mixture of many substances produced by many different cells (in the stomach and duodenum both by epithelial cells and by the goblet cells) and its secretion is influenced by many factors: the local application of acid to the antral mucosa greatly increases its mucus production, while steroids,[18] e.g. ACTH, given parenterally, decrease it.

Direct local application of prednisone to the gastric mucosa causes no detectable changes, but its systemic action significantly decreases mucus secretion and this may account for at least part of the ulcerogenic action of steroids. Cortisone not only diminishes the amount of mucus secreted, but affects its biochemical composition by decreasing its sialic acid concentration.[19] Other therapeutic agents which may cause gastric erosions or ulceration, e.g. aspirin, phenylbutazone and indomethacin, may act similarly, so that if these could be combined with a mucus-stimulating drug, it would constitute a considerable therapeutic advance.

I believe that this mucin mechanism may explain the 120-year-old mystery of the Curling ulcer which follows burns and may possibly occur more often than is recognized.[25] Shock due to severe burns may last for days or even weeks and increases blood-cortisol levels to 3 or even 4 times the normal values. As judged by evidence so far available this would depress gastroduodenal mucus secretion and thus might account for the development of erosions or ulceration. It has been conclusively shown[21] in animals that gastric mucus is grossly reduced after burns, and it may be that prophylactic carbenoxolone should be tried in cases of severe burns since antacids certainly do not prevent erosions or ulceration.[22]

James[14] has shown the increase of mucus-producing cells in the duodenum in response to the stimulus of high acid concentrations in cases of duodenal ulcers. The findings are most striking in the Zollinger-Ellison syndrome —a type of natural tissue response in which the normal duodenal absorptive cells appear to become changed into protective cells.

A great deal of experimental work[16] has shown that carbenoxolone does in fact stimulate the secretion of mucus. Clearly, if mucin is to form a protective layer on the surface of the mucosa it must be there in some form that makes it adherent to the cells to prevent its being

constantly washed away, or it has to be secreted so continuously and in such enormous amounts that it is able to act as a barrier despite its perpetual removal. It seems probable that carbenoxolone may be concerned in both the above mechanisms, i.e. an increased mucus production and an increased retention of mucus at the surface of the cells. Some chemical change in the type of mucus produced may also be involved, there being some evidence that carbenoxolone alters the proportion of acid-repellant mucopolysaccharide as compared with the non-acid repellant. This action of carbenoxolone is mainly upon the surface of the mucosa and not via the blood stream after absorption. It has a protein-binding effect, so that when in contact with the mucosa it induces mucin synthesis and this mucin adheres to the surface where it is being extruded. This action could explain how a short-lasting contact of carbenoxolone with an ulcer surface might be enough to make the mucus protective layer remain adherent. Johnson[15] has shown that the 'fuzzy' layer on the cell surface is apparently increased by carbenoxolone, and it may be that this sponge-like adherent mesh may retain alkaline secretions which help to protect the mucosa against acid and pepsin digestion.[26] The superficial layer of mucin formed at the apical poles of the secretory cells is rich in sulphated glycoproteins, and this, in combination with protein on the cell surface, could form a coating highly resistant to the action of pepsin on these cells.[16] The cell turnover rate of mucosal cells is, however, very rapid, and so it is unlikely that such a mucus layer would remain many hours *in situ* and that repeated fresh contact with carbenoxolone would be required for continual protection. The history of peptic ulceration suggests some intermittent breakdown in mucosal protection, and conversely, to obtain full healing, continuous protection. At present it is not known how long artificial protection by carbenoxolone may be necessary to maintain or increase mucosal resistance, i.e. to prevent recurrence of ulceration after healing has occurred. Should protection with carbenoxolone be maintained by indefinite administration, or can the factors which determine recurrence somehow be discovered? It is upon this prevention of recurrence that the true management of peptic ulcer depends, and it will require many more cases and a much longer period of trial before we shall know how far carbenoxolone may prove to be a means of achieving this.

SUMMARY

Some account is given of carbenoxolone sodium which is regarded as an accepted and valuable aid in the ambulant treatment of gastric ulcer patients. Trials of a specially prepared capsule (Duogastrone) containing carbenoxolone suggest that in this form the drug may also provide a useful treatment for duodenal ulcer. Evidence suggests that its mode of action is by stimulating mucin production, and through its protein-binding effect to produce a protective layer over the ulcer. No results of long-term treatment for duodenal ulcer are yet available and more work will be needed to assess this. The drug is rapidly absorbed from the stomach where it acts locally and not systemically. Side-effects, which may take the form of sodium retention or potassium depletion, are discussed.

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