Ultrastructural Changes in Gastric Ulcers after Bicitropeptide and Cimetidine Treatment

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SUMMARY

Ultrastructural studies were conducted on biopsy specimens taken by endoscopy from the edge of gastric ulcers in the distal part of the stomach of 9 patients before and after treatment with either bicitropeptide or cimetidine. Marked depletion of mucin granules in the mucous epithelial cells and the pyloric gland cells was found in all patients and there was morphological evidence of a block in the synthesis of mucus glycoproteins. This block was located in the Golgi region of these cells. Synthesis of structurally normal mucin granules was restored after treatment with either bicitropeptide or cimetidine.


According to the results of recent studies, the drugs cimetidine (Tagamet; Smith, Kline & French) and bicitropeptide (BCP-Compound; Scherag) are superior to a placebo in the treatment of gastric ulcers. The modes of action of the above drugs are, however, different. Cimetidine inhibits gastric acid production, while bicitropeptide is claimed to protect the ulcerated areas against pepsin and gastric acid.

The question arose whether or not the above difference in mode of action is reflected in the histological changes taking place during recovery of the ulcerated tissues. It was therefore considered of interest to investigate, by means of the electron microscope, specimens obtained from the ulcer before, during and after treatment with the above drugs.
PATIENTS AND METHODS

A total of 9 patients (7 women) between 31 and 60 years of age was investigated. All members of the group had, for periods varying from 18 months to 10 years, complained of gastric symptoms. Immediately before treatment the complaints were such that endoscopic examination appeared justified in all cases. Invariably one or more ulcers were diagnosed, these being 3 - 10 mm in diameter and situated in the distal half of the stomach. Two patients, one from each of the two experimental groups, also had duodenal ulcers.

Specimens were obtained from the rim of the ulcer during endoscopic examination, before and after treatment. Cimetidine treatment (200 mg three times during the day plus 400 mg in the evening for a period of between 43 and 49 days) was given to 1 male and 2 female patients who were between 31 and 43 years of age. The remaining 6 patients (2 males and 4 females between 33 and 60 years of age) received bicitropeptide (2 teaspoonsful mixed with 6 teaspoonsful of water) 1 hour before mealtimes and also in the evenings for between 40 and 57 days. After starting treatment, specimens were taken from the areas where ulcers had originally been located. Histological material was obtained after a period of 17 - 24 days of treatment from 6 patients (3 from each group).

No special diets or sick leave were prescribed and the patients remained ambulant during treatment. For effective bicitropeptide treatment the acidity of the gastric content had to be left unchanged. Consumption of small amounts of food, antacids and buffering drinks such as milk between meals was therefore prohibited.

All biopsy specimens were fixed immediately in ice-cold 2.5% glutaraldehyde in 0.1M cacodylate buffer at pH 7.2 for 2 hours followed by post-osmication (1% cacodylate-buffered osmium tetroxide), dehydration and embedding in Epon-Araldite. Thin sections were stained with uranyl acetate and Reynold's lead citrate and examined in a Philips 301 electron microscope.

RESULTS

Symptoms

All patients reported disappearance of symptoms — patients on cimetidine within 2 - 10 days and those on bicitropeptide within 3 - 14 days.

Endoscopic Examination

Improvement was observed in all patients. In 2 patients in the cimetidine group no ulcers were detected at endo-

![Fig. 3](image1.jpg) A pyloric gland of a patient before treatment shows marked depletion of mature mucin granules (arrows). The microvilli (MV) appear normal ($\times$ 12 500).

![Fig. 4](image2.jpg) Same patient as in Fig. 3, after treatment with cimetidine. There is a marked increase in mucin granules (circles) in the apical cytoplasm of pyloric glandular cells ($\times$ 7 500).
Endoscopy performed after 3 and 6 weeks of treatment. Before treatment the third patient had five ulcers varying in diameter from 2 to 5 mm. Endoscopy after 17 days' treatment revealed one ulcer of only 2 mm in diameter. This ulcer remained unchanged up to termination of treatment at 45 days.

After 3 weeks of treatment with bicitropeptide, 3 of the 6 patients still had their original ulcer; the area of ulceration, however, was considerably smaller than before treatment. In 1 of these patients the ulcer was still unchanged after 43 days, and in another after 56 days. In the third patient the ulcer was completely healed after 57 days. The remaining 3 patients were examined between 40 and 42 days after initiation of treatment. Two had completely recovered, while one small ulcer was still to be seen in the third patient.

Electron Microscopy

The biopsy specimens were all taken from distal parts of the stomach. Since these stomach areas contain mainly surface mucous cells and pyloric gland (mucous) cells, the following description will emphasize structural changes in these cells.

Before treatment, the main granules of the surface mucous cells of all patients had a coarsely granular appearance and there was marked depletion of dense, homogeneous, presumably mature mucin granules (Fig. 1). These findings were in marked contrast to the appearance of large numbers of homogeneously dense, mature mucin granules in surface epithelial cells of all patients after treatment with either cimetidine or bicitropeptide (Fig. 2).

This marked depletion of mature mucin granules was also clearly evident in the pyloric gland cells of all patients before treatment (Fig. 3), while treatment with either cimetidine or bicitropeptide led to the formation of large numbers of mature, dense granules in the superficial parts of the cytoplasm of glandular cells (Fig. 4). In addition, the cells of the pyloric glands showed changes which we interpreted as evidence of a block in the synthesis of mucus glycoproteins. These changes consisted of the appearance of large, confluent masses of finely granular material in the Golgi region of these cells (Fig. 5) and in the apical cytoplasm adjacent to the glandular lumen. This was in marked contrast to the appearance of discrete, dense granules with closely applied limiting membranes found in gland cells of patients after treatment with either drug (Fig. 6).

Other changes, not related to mucous cells, which were found in most patients before treatment, were the

**Fig. 5.** Patient before treatment: confluent masses of finely granular material (asterisks) are found in the Golgi region (G) of a pyloric glandular cell (N = nucleus) (× 15 100).

**Fig. 6.** Same patient as in Fig. 5, after treatment with BCP: discrete, dense mucin granules (arrows) are seen (× 22 500).
following: (i) increased mitotic activity in surface epithelial cells (Fig. 7) and (ii) marked infiltration of neutrophil polymorphs and plasma cells in the lamina propria (Fig. 8). The leucocytes also infiltrated the epithelial layer (Fig. 8), but after treatment no neutrophils were found in the epithelium or lamina propria and the latter only contained large numbers of plasma cells (Fig. 9). Endocrine cells, presumably G cells, showed no significant abnormalities (Fig. 10).

**DISCUSSION**

In the present study of gastric ulcers from the distal region of the stomach, the most significant ultrastructural changes were found in the mucin granules of the surface epithelial cells and of the pyloric glands. These changes consisted essentially of depletion of mature mucin granules with accumulation of mucus glycoproteins in Golgi membranes during the acute stage of gastric ulceration. After treatment with either cimetidine or bicarbonate the morphological features were comparable to those described in the normal human gastric mucosa. The abnormal microvilli which have been described by other investigators in duodenal ulcers and which did not return to normal even after long-term treatment with cimetidine were never seen in our patients with gastric ulcers. This is not surprising, since the normal cells of the stomach do not have the regular, closely packed microvilli of the normal duodenum.

In patients with gastric ulcers and intestinal metaplasia of the gastric mucosa, histochemical and antigenic differences between mucus glycoproteins isolated from normal and intestinalized gastric mucosae have been described. Furthermore, biochemical analyses of isolated glycoproteins from normal and intestinalized gastric mucosae have shown that all the glycoproteins were qualitatively similar, but differences were found in the quantitative relationships between the four monosaccharides: galactose, fucose, N-acetylgalactosamine and N-acetylgalactosamine. In our patients intestinal metaplasia was not a significant feature. Our results would seem to indicate that under these conditions structurally normal mucus glycoproteins are synthesized, but that mature mucin granules are formed at a decreased rate, as evidenced by the marked depletion of these granules. Ribosomal synthesis of mucus glycoproteins was followed by concentration and further glycosylation of these macromolecules in Golgi membranes. Appearances such as those shown in Fig. 5, i.e. accumulation of finely granular material in Golgi membranes, suggest that these Golgi functions of
concentration, glycosylation and storage of glycoproteins were suboptimal and therefore constituted a block in the formation of 'mature' mucus.

Other ultrastructural changes such as increased mitotic activity of epithelial cells and infiltration of neutrophils and plasma cells in the lamina propria probably constituted a reaction to injury and formed part of the inflammatory response. Infiltration by plasma cells was also a prominent feature in intestinalized gastric mucosae.

We wish to thank Scherag (Pty) Ltd for providing the drugs, and Mr C. N. Henning and Miss S. Kempff for technical assistance.

REFERENCES