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The antral gastrin-producing cells in duodenal ulcer patients

A light microscopic and ultrastructural study during long-term, low dose treatment with cimetidine

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Summary. The antral mucosa has been examined in four duodenal ulcer patients before and during long-term, low dose treatment with cimetidine (given a total dose of between 472 g and 894 g). No convincing changes were found in the number or the volume of G cells. Signs of inactivity were demonstrated ultrastructurally, with small granules of intermediate type, a reduced amount of granular endoplasmatic reticulum and Golgi complex, mostly showing no signs of granulogenesis. The occurrence of bundles of cytoplasmic microfilaments, not observed before treatment and the reduced number of D cells may also be signs of inactivity. Hyperplasia and/or neoplasia were not seen in other antral endocrine cells.

Key words: Cimetidine – Duodenal ulcer – Gastrin producing cells – Long-term treatment

Introduction

Histamine H2-receptor antagonists are widely used in the treatment of chronic duodenal ulcer and in many cases the treatment is continued at a low dose for a number of years.

In the present investigation a search has been made for changes in the antral endocrine cells, with special reference to gastrin-producing cells (G cells) during long-term, low dose treatment with cimetidine.

Material and methods

The material comprises four men (81,77, 56 and 67 years of age), with endoscopically confirmed chronic duodenal ulcer disease. All four patients had been on low dose cimetidine treatment (400 mg at night) for at least two years. Prior to this, all had received full dose treatment (1 g daily) for at least two, one month courses. All developed recurrence of the condition after cessation of the full dose treatment. The total doses of cimetidine were 472 g, 586 g, 876 g and 894 g, respectively.

Biopsies from the antral mucosa were obtained, endoscopically, roughly 2 cm orally to the pyloric ring (after 8 h of fasting) before and during long-term treatment.

Three biopsies were examined in the light microscope. G cells were identified using the indirect immunoperoxidase technique (Nielsen et al. 1979). Silver staining, using the method of Masson-Hamperl and Grimelius, was used for argentaffin and argyrophil cell identification (Grimelius and Wilander 1980). The G cells were quantified as previously described (Nielsen et al. 1980a). The number of argentaffin and argyrophil stainded cell profiles was counted at a magnification of ×400, after systematic selection of fields of vision. The results are given as the mean value of counts in at least five fields of vision.

Four biopsies were used for the ultrastructural analysis. The biopsies were immediately fixed in 5% cold glutaraldehyde, buffered at pH 7.4 by means of 0.2 M Na-cacodylate. The specimens were post-fixed in 1% osmium tetroxide, dehydrated and embedded in epon. Thick sections (4 μm) from each biopsy were stained with toluidine blue for orientation. The number of thick sections was so large that at least one area from each biopsy included the terminal, middle and basal part of the mucosa, the areas subsequently selected for the ultrathin sections. Any area exhibiting intestinal metaplasia was excluded. The ultrathin sections (60–80 nm) were counter-stained with lead citrate and Zn-uranyl acetate and examined in a Philips EM 201C electron microscope. At least 50 ultrathin sections were examined from each biopsy, all endocrine cells were identified and photographed. The number of each endocrine cell type was estimated per 200 photographs.

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Results

Light microscopy

It can be seen from Table 1 that no changes in the quantity of G cells were found during long-term treatment with cimetidine. Neither were there any convincing changes in the number of argentaffin or argyrophil stained cells.

Table 1. G cell densities, argentaffin and argyrophil stained cell profiles before and during long-term treatment of four duodenal ulcer patients. Volume density (V_V) in %, numerical density (N_V) as cells/mm^3, mean cell volume ($\bar{V}$) as μm^3

	Cimetidine grams	G cells V_V	G cells N_V	G cells $\bar{V}$	Argentaffin cells arbitrary units	Argyrophil cells arbitrary units
No. 1	0	2.7	21308	1267	0.20	1.75
	472	2.2	18755	1173	0.09	1.20
No. 2	0	1.8	18607	967	0.06	1.33
	586	1.5	16801	893	0.05	1.50
No. 3	0	2.2	18303	1202	0.18	0.92
	876	2.3	17401	1319	0.10	1.15
No. 4	0	1.9	20914	909	0.08	1.05
	894	2.2	24512	898	0.14	0.86

Electron microscopy

Five different types of endocrine cells could be identified: G (Fig. 1) – EC – D – D-1 and small granulated gastric P-like cells (Solcia et al. 1980). No obvious differences were found in the number of EC, D-1 and P-like cells following treatment, but the number of D cells was markedly reduced from more than 15/200 per photograph to 0-2/200 per photograph. The ultrastructure of the endocrine cells, except for the G cells, remainded unaltered during the treatment period.

The changes observed in the G cells were mainly in the secretory granules which were rather small and angulated. Most of the granules were of the intermediate type, containing a loose core of floccular or filamentous material. The dense cored granules were very polymorphic, partly because of a reduced amount of electron dense material. This was also situated excentrically within the granule membrane. In addition to these changes in the morphology of the granules, bundles of cytoplasmic microfilaments, often with a perinuclear localization were observed in many of the cells (Fig. 2). The granular endoplasmic reticulum was sparse (Fig. 3), and the Golgi complex rarely showed signs of granulogenesis. Dense bodies, with or without lipid droplets, could be found, but lysosomes with signs of granulocytosis were never observed. Similarly, there was no evidence of exocytosis, neither before nor during long-term treatment.

Discussion

Prolonged treatment of duodenal ulcer patients with low dose (400 mg at night) cimetidine did not appear to maintain nor increase antral G cell hyperplasia, as described after treatment with the normal dose (1 g daily) for eight weeks (Nielsen et al. 1980b). The increased G cell activity during

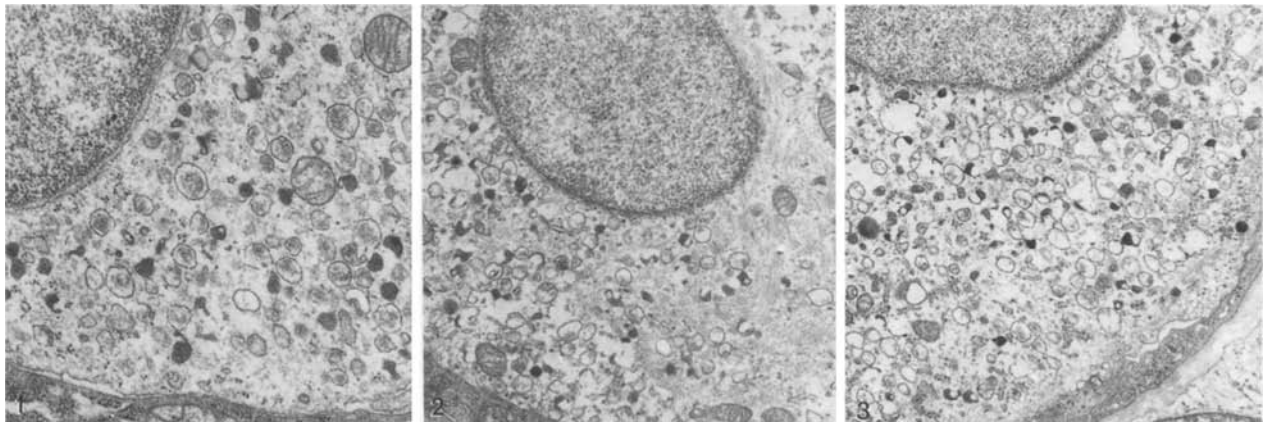

Fig. 1. Antral G cell prior to treatment with cimetidine, containing granules almost all of which are of the intermediate type. No cytoplasmatic microfilaments are seen. ×12000

Fig. 2. Antral G cell during long-term treatment with low dose cimetidine (400 mg at night). Most granules are of the intermediate type. Bundles of cytoplasmic microfilaments can be seen perinuclearly on the right side. No endoplasmic reticulum or Golgi complex are seen. ×7200

Fig. 3. Antral G cell during long-term treatment with low dose cimetidine (400 mg at night). As in Fig. 2 most granules are of the intermediate type with sparse floccular material. The few dense cored granules are very polymorphic with regard to shape with the material situated excentrically within the granule membrane. The endoplasmic reticulum is spares (bottom of the cell). ×7200

normal dose treatment could not be demonstrated during long-term, low dose treatment (Nielsen and Hage 1985). In contrast, the following ultrastructural signs of inactivity were found: the granules were of the intermediate type, the dense cored granules were polymorphic, due to a reduced amount of electron dense material, there were bundles of cytoplasmic microfilaments, the granular endoplasmic reticulum was sparse and the Golgi complex rarely showed signs of granulogenesis. Lysosomes, a constant feature of normal dose treatment believed to be involved in the destruction of superfluous gastrin components produced during hyperactivity (Nielsen and Hage 1985), were not seen during long-term treatment.

As D cells are believed to be local modulators of gastrin secretion, the reduced number of D cells observed may also be related to the inactivity of the G cells (Gustavsson and Lundqvist 1978; Uvnäs-Wallensten et al. 1977).

Unfortunately, no measurements are available of the serum gastrin levels before treatment. The basal serum gastrin was measured in three of the four patients during long-term, low dose treatment and was found to be very low (0, 6 pmol/l and 15 pmol/l, respectively).

The finding of G cell inactivity and no changes in the number of G cells in the present study are in contrast with the findings in patients with achlorhydria or hypochlorhydria, caused by atrophic gastritis, not affecting the antral mucosa (Korman et al. 1973; Stockbrügger et al. 1977), it also contrasts with the marked increase in the number and size of the antral G cells seen in long-term examination of the antrum mucosa after selective proximal vagotomy and pyloroplasty (Holle et al. 1985). The G cell hyperplasia and hypergastrinaemia in these patients can be explained by the fact that the inhibition of the G cells by acid is absent. Studies on rats have suggested that marked G cell hyperplasia during treatment with cimetidine can be prevented by normal basal acid secretion during the daytime, although a marked reduction in both basal and pentagastrin stimulated acid secretion can be seen at night (Griffiths and Morris 1984). This might also explain why we did not find G cell hyperplasia, but does not appear to explain the ultrastructural findings of inactivity. There are two alternatives, either a direct action of long-term treatment of cimetidine on the G cells, or an indirect action of cimetidine via paracrine influence from the D cells.

In conclusion, long-term, low dose treatment of duodenal ulcer patients with cimetidine, does not cause hyperplasia nor neoplasia of the G cells, or other antral endocrine cells, but produces G cell inactivity.

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