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The effects of omeprazole and famotidine on mucin and PGE_2 release in the rat stomach

K. YOSHIMURA, S. G. DELBARRE, E. KRAUS & C. R. BOLAND
Department of Internal Medicine, VA Medical Centre and The University of Michigan School of Medicine Ann Arbor, Michigan, USA

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SUMMARY

Background: Gastric antisecretory agents may inhibit the synthesis or secretion of gastric mucin during acid suppression, which would interfere with mucosal protection and limit the efficacy of the agents.
Methods: Rats were dosed with famotidine, omeprazole, or buffer control for 4 weeks. Mucin synthesis, mucin histochemistry, mucin carbohydrate composition and prostaglandin E_2 (PGE_2) release were measured during and after drug treatment.
Results: PGE_2 release was maximally inhibited after 2 weeks of omeprazole or 4 weeks of famotidine. Total glycoprotein synthesis was inhibited at all times by omeprazole, but only after the cessation of dosing with famotidine. Sulphated glycoprotein synthesis was inhibited by both drugs at 2 weeks. PGE_2release and sulphated glycoprotein synthesis were restored to control values or more by the 5th day after the end of dosing, at which time total glycoprotein synthesis was significantly suppressed in both groups. Histologically, a reduction of PAS-positive surface mucus was observed after 2 weeks of dosing in both groups. Both famotidine and omeprazole reduced the sialic acid content during and after treatment.
Conclusions: These results suggest that long-term anti-secretory therapy also affects the production of factors involved in primary gastric mucosal defence, which should be considered in the assessment of response to treatment in clinical trials.

INTRODUCTION

The balance between defensive and aggressive factors in the stomach has been proposed as an important component in the aetiology of peptic ulcer disease.[1] However, the mechanisms that regulate the production of acid, pepsin and mucosal defence appear to be interrelated, and perturbation of one factor may influence another. For example, Yamamoto *et al.* have shown that acid suppression by omeprazole and cimetidine is dose-dependently accompanied by a reduction of pepsin output in the rat stomach.[2] Takeuchi *et al.* have reported that exogenously added pepsin produced a significant increase in frog gastric mucus thickness.[3] In addition, it has been shown by Ryberg *et al.* that 1 week of treatment with ranitidine and omeprazole caused a significant increase in plasma gastrin levels in the rat stomach.[4] Pique *et al.* have demonstrated a linear correlation between increments in acid output and increments in mucosal blood flow as they increased the dose of pentagastrin in rats.[5] However, little is known about the influence of gastric acid suppression induced by H_2-receptor antagonists or proton pump inhibitors on the defensive factors in the stomach, such as mucin production. We tested the hypothesis that long-term treatment with these drugs may affect mucin synthesis and prostaglandin E_2 release in the stomach.

Correspondence: Dr C. R. Boland, Division of Gastroenterology, University of California, San Diego, Department of Medicine, School of Medicine, 2055 Cellular and Molecular Medicine East, 9500 Gillman Drive, La Jolla, CA 92093–0688, USA.

MATERIALS AND METHODS

Reagents

Famotidine (Pepcid) and omeprazole (Prilosec) were obtained from Merck Sharp & Dohme (West Point, PA).

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Gentamicin was obtained from Flow Laboratories Inc. (McLean, VA). DME (Dulbecco's modified Eagle's medium) F-12 (1:1) tissue culture medium with L-glutamine and 15 mM HEPES (N-2-hydroxyethylpiperazine-N′-2-ethanesulphonic acid), ribonuclease-A, deoxyribonuclease-I, monosaccharides for standards in the carbohydrate analysis, and sodium acetate were purchased from Sigma Chemical Company (St Louis, MO); trichloroacetic acid (TCA) and 50% (w/w) glucosamine hydrochloride (1.04 TBq/mmol) from Amersham Corporation (Arlington Heights, IL); ^{35}S (sulphur-35, 59.2 TBq/mmol) from New England Nuclear Products (Boston, MA); diethyl ether from Mallinckrodt Inc. (Paris, KY); 100% ethyl alcohol from Midwest Grain Products Co. (Weston, MO); EcoLite(+) from ICN Biomedicals Inc. (Irvine, CA); trifluoroacetic acid (TFA) from Pierce (Rockford, IL); caesium chloride (99.99% purity) from Schwarz/Mann (Cleveland, OH). The chromatographic separations were performed on a Dionex BioLC gradient pump module with a model PAD 2 detector, and the monosaccharide separation performed on a 4.6 × 250 mm HPIC-AS6 anion-exchange column equipped with an AG-6 guard column (Dionex, Sunnyvale, CA).

Drug administration and dose selection

Male Wistar rats, weighing 160–180 g, were used in this study according to the VA Animal Usage Protocol. Famotidine (FAM) at 4 mg/kg suspended in 4 mM $NaHCO_3$ (pH 8.0), omeprazole (OME) at 30 mg/kg suspended in 4 mM $NaHCO_3$ (pH 8.0), or control buffer, was administered by oral gavage to rats once daily. Rats were fasted overnight before the experiments but allowed free access to water.

The dose of omeprazole was selected on the basis of the reported experience of Yamamoto *et al.*[2] Omeprazole produces a dose-related decrease in gastric secretory volume, acid output, pepsin output, and gastric damage in response to stress when administered in doses range from 3 to 100 mg/kg. A dose of 30 mg/kg decreases gastric acid output to less than 20% of control values without evidence of toxicity, and was selected for use. Famotidine was selected as a long-acting H_2-antagonist that could be administered by gavage once a day. Yamamoto *et al.* demonstrated that cimetidine (at a maximum dose of 200 mg/kg) decreased the acid output to 50% of control levels.[2] Since the clinically relevant dose of cimetidine in humans is at least 50–60 times as high as that for famotidine, a dose of 4 mg/kg of famotidine was selected for this study.

Tissue culture

After 2 or 4 weeks of dosing, and 5 days after the end of 4 weeks of dosing, rats were killed by cervical dislocation 2–3 h after the last dose. The stomachs were immediately excised and the muscular layer was removed from the fundus. The mucosal layer was cut into small pieces of uniform size and shape (2 × 2 mm) using a series of blades held in a frame to cut the tissue. The pieces were weighed to test for uniformity, and groups of 10 were found to differ in mass by less than 5%. Ten tissue pieces were placed in each plastic culture well (diameter 35 mm) with 2 mL of medium consisting of DME/F12 (1:1) L-glutamine, 15 mM HEPES, 10% foetal bovine serum (FBS) and 0.05 mg/mL gentamicin.[6] The explants were incubated in the presence of 5 μCi/well D-[1,6-^{3}H]-glucosamine or 5 μCi/well ^{35}S at 37 °C under 5% CO_2/95% air. Wells were also maintained in the absence of radioactivity for the measurement of PGE_2.

Measurement of PGE_2

Fifty microlitres of media was collected from each unlabelled well before (i.e. immediately after placement in culture) and after 3 h incubation, and immediately frozen at −70 °C. PGE_2 in media was quantified by radioimmunoassay (RIA) in the University of Michigan Diabetes Centre Ligand Core Laboratory.[7]

The PGE_2 antibody was purchased commercially from Cayman Chemical Co. (Ann Arbor, MI). Cross reactivities with other prostaglandins are as follows: 15-keto-PGE_2: 9.2%, and PGE_1: 5%. Cross reactivities were less than 0.2% for the following prostaglandins: PGA_1, PGB_1, PGB_2, PGD_2, $PGF_{1\alpha}$, 6-keto $PGF_{1\alpha}$ $PGF_{2\alpha}$ 13,14-dihydro-15-keto-$PGF_{2\alpha}$, and thromboxane B_2 (manufacturer's specifications). PGE_2 generation was calculated by subtracting time 0 from the 3-h value to correct for carry-over during tissue preparation.

Assessment of glycoprotein synthesis

At the end of 6 h of incubation with ^{3}H-glucosamine or ^{35}S, media and tissue fragments were harvested together. After homogenization and sonication, they were centrifuged at 100 000 *g* at 4 °C for 1 h to remove cellular

debris. The supernatant was precipitated with 10% TCA and 1% PTA at 4 °C overnight. Then, the samples were centrifuged at 500 *g* for 25 min and the pellets were resuspended by sonication. Each pellet was washed threefold with 10% TCA/1% PTA and twice with ether/ethanol.[31] The pellets were dissolved in 2 mL of 0.6 M KOH and ^{3}H- or ^{35}S-radioactivity was measured by liquid scintillation counting.[8]

Purification of mucin and carbohydrate analysis

Five rats were dosed in each group at each time point. After 4 weeks of dosing, and 5 days after the end of the 4 weeks' dosing, the fundus was removed and the mucosa was homogenized and sonicated in phosphate-buffered saline (PBS), pH 7.4, to disrupt cells. The resulting suspensions were centrifuged at 38000 r.p.m. (100000 *g*) for 1 h at 4 °C. The supernatants were applied to a 5 × 100 cm glass column packed with Sepharose CL-4B, equilibrated with PBS, and eluted at a flow rate of 60 mL/h. The void volume peak, which contained the mucin-rich fraction, was pooled, dialysed exhaustively against deionized water and lyophilized. The samples were digested with protease-free bovine deoxyribonuclease (DNase)-I and bovine ribonuclease (RNase)-A for 16 h at 37 °C in PBS, pH 7.4, containing 10 mM $MgCl_2$ and 0.02% NaN_3; 1 mg of each nuclease was added for each 5 mg of mucin. The digest mixture was centrifuged at 10000 r.p.m. (15000 *g*) for 30 min to remove the resulting precipitate, and the supernatant was dialysed against PBS at 4 °C. Subsequently, 12.9 g of CsCl was added to the dialysed material and the final volume adjusted to 24 mL (starting density, 1.38 g/mL). The samples (2 × 12 mL tubes) were centrifuged at 36000 r.p.m. (100000 *g*) for 48 h at 4 °C. After the gradient had formed, 8 × 1.5-mL fractions were collected by aspiration and weighed to determine their specific gravity (SG). Fractions 5–7 (SG: 1.35–1.45 g/mL) were pooled together, dialysed to remove CsCl and PBS salts, and lyophilized. The sample was hydrolysed and applied to a high performance liquid chromatography ion exchange column with pulsed amperometric detection (Dionex) for carbohydrate analysis as described previous.[9]

Histological evaluation

After 2 or 4 weeks of dosing, and 5 days after the end of 4 weeks of dosing, the stomachs were excised and the oxyntic mucosa was cut into 2 mm wide tissue strips and preserved in neutral, buffered 4% formaldehyde solution. After dehydration, the specimens were embedded in paraffin, sectioned at 5 μM, and stained with haematoxylin-eosin or PAS-Alcian blue.[10]

Statistical analysis

The results are expressed as means ± s.e. *N* is the number of rats used in each experiment. Statistical analysis was carried out using Student's *t*-test. *P*-values of less than 0.05 were considered to be significant.

RESULTS

Prostaglandin E_2 release

The results of each assay are expressed as a percentage of control wells at each time point. As shown in Figure 1, PGE$_2$ release was initially inhibited after 2 weeks of OME (43 ± 4%, $P < 0.001$) and 4 weeks of FAM (69 ± 8%, $P < 0.01$), but recovered to a level greater than measured in control wells by the 5th day after the end of dosing in both groups.

Glycoprotein synthesis

The results of each assay are expressed as a percentage of control wells at each time point. Total glycoprotein synthesis, which is expressed as ^{3}H-glucosamine in-

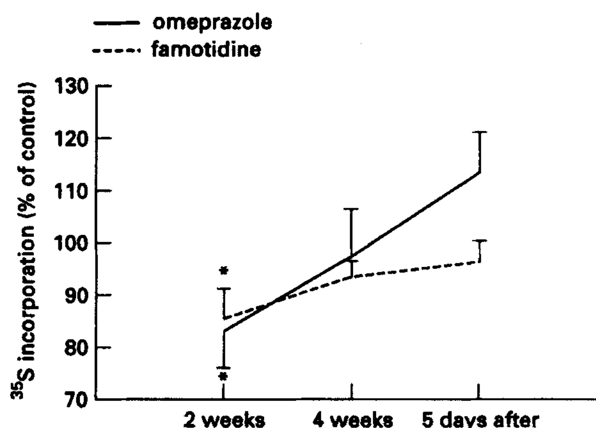

Figure 1. PGE$_2$ release after 2 or 4 weeks dosing with 4 mg/kg FAM and 30 mg/kg OME, and 5 days after the end of 4 weeks of dosing, measured by radioimmunoassay (RIA). The values are expressed as a percentage of control wells at each time point. ($n = 5$; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, compared with control.)

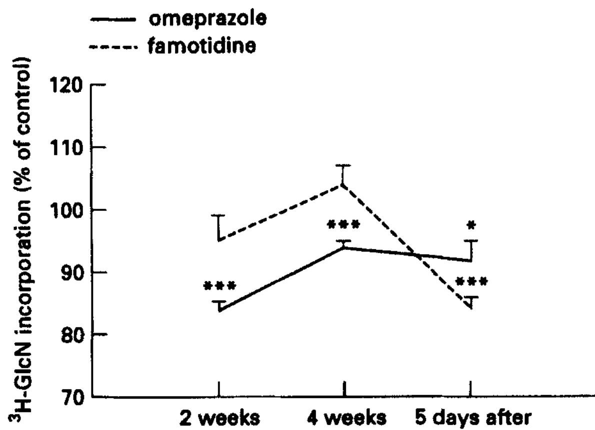

Figure 2. ^{3}H-glucosamine incorporation into fundic tissues and new glycoprotein synthesis after 2 or 4 weeks of dosing with 4 mg/kg FAM and 30 mg/kg OME, and 5 days after the end of 4 weeks of dosing, measured by glycoprotein precipitation using 10%TCA/1%PTA and lipid extraction. The values are expressed as a percentage of control wells at each time point. (n = 5; *P < 0.05, ***P < 0.001, compared with control.)

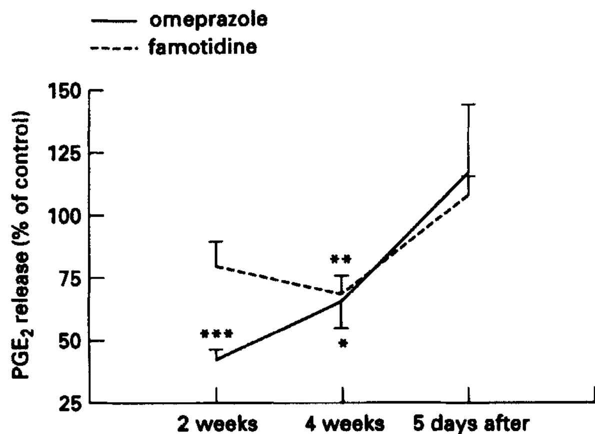

Figure 3. ^{35}S incorporation into fundic tissues and new glycoprotein synthesis after 2 or 4 weeks of dosing with 4 mg/kg FAM and 30 mg/kg OME, and 5 days after the end of 4 weeks of dosing, measured by glycoprotein precipitation using 10%TCA/1%PTA and lipid extraction. The values are expressed as a percentage of control wells at each time point. (n = 5; *P < 0.05)

corporation, is shown in Figure 2. Total glycoprotein synthesis was significantly suppressed at all time points by OME (84±1% to 94±1%), but suppression was observed only after the cessation of dosing with FAM (84±2%). As shown in Figure 3, sulphated glycoprotein synthesis was initially significantly inhibited after 2 weeks of dosing in both groups (83±7% for OME, 85±6% for FAM-treated group) but synthesis recovered

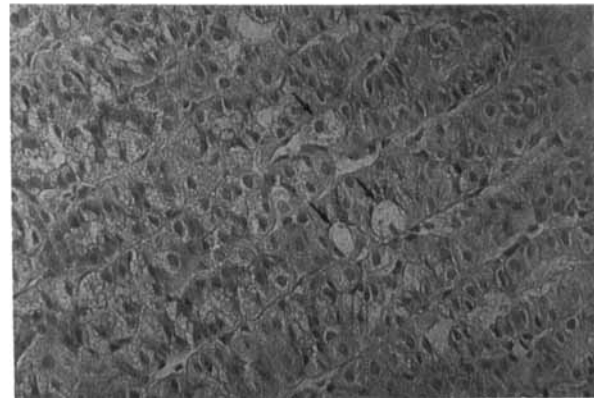

Figure 4. Characteristic vacuolar degeneration of parietal cells (arrowheads) is observed after 2 weeks of dosing with 30 mg/kg OME, stained with haematoxylin-eosin. (×400)

to control values or more by the 5th day after the end of dosing in both groups.

Histological evaluation

Vacuolation of parietal cells was observed at all time points in both dosed groups, however, most remarkably present after 2 weeks of dosing with OME as shown in Figure 4. As shown in Figure 5, PAS-positive surface mucus production was reduced after 2 weeks of dosing with OME and FAM. The reduction was not observed at other time points in either treated group.

Carbohydrate composition

The carbohydrate composition data are expressed as a percentage of total carbohydrate content for each monosaccharide. Whereas there were only minor changes in the relative compositions of the neutral sugars, sialic acid content fell dramatically during and after dosing with OME and FAM (Table 1).

DISCUSSION

H_2-receptor antagonists and proton pump inhibitors are widely used for gastric acid suppression, and the elimination of acid is considered the most effective therapy for peptic ulcer diseases. However, it is also known that the recurrence rate of ulcers is rather high after initial healing with those drugs.[11] In addition, little has been known about the effect of long-term treatment with these drugs on the defensive factors in the stomach, such as mucin production. In this study, therefore, we tested the

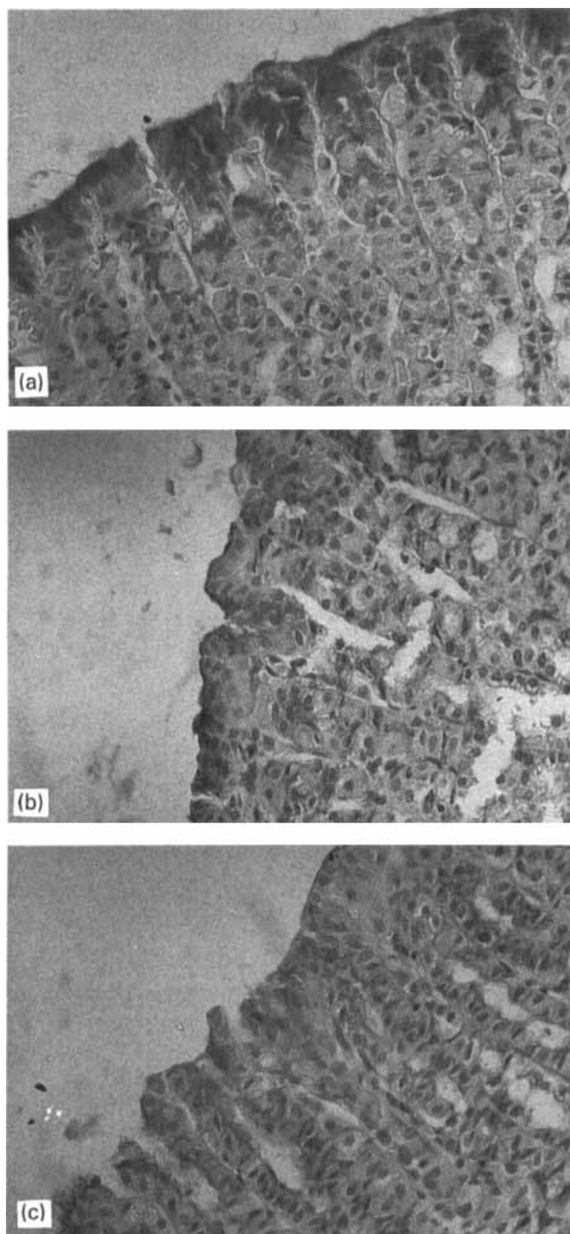

Figure 5. PAS-positive surface mucus production is remarkably reduced after 2 weeks dosing with 4 mg/kg FAM and 30 mg/kg OME; stained with PAS-alcian blue. (a) control, (b) FAM- and (c) OME-dosed fundic mucosa. ($\times$ 400)

hypothesis that long-term treatment with omeprazole and famotidine may affect mucin production and PGE_2 release in the stomach, and found that changes in PGE_2 and glycoproteins were produced by these agents.

Baker *et al.* have demonstrated that there are significant correlations between the output of gastric acid and gastric outputs of PGE and PGF in response to intravenous infusions of pentagastrin, histamine and in-

Table 1. Carbohydrate composition of fundic mucin during and after dosing with FAM and OME

Group	Fuc	GalNAc	GlcNAc	Gal	SA
Controls	17.15	12.13	37.06	32.41	1.25
FAM (4 weeks)	17.50	6.00	41.33	34.87	0.30
FAM (5 days after)	21.43	6.16	38.44	33.85	0.12
OME (4 weeks)	21.17	9.57	37.58	31.64	0.04
OME (5 days after)	19.09	11.63	35.52	33.46	0.30

Carbohydrate composition of fundic mucin after 4 weeks treatment with 4 mg/kg FAM and 30 mg/kg OME, and 5 days after the end of the 4 weeks of dosing.
The results are expressed as a percentage of total carbohydrate content for each monosaccharide.
Abbreviations: Fuc: fucose; GalNAc: *N*-acetylgalactosamine; GlcNAc: *N*-acetylglucosamine; Gal: galactose; SA: sialic acid

sulin in cat gastric juice, and have also shown that a significant correlation is observed between pepsin output and endogenous PGE and PGF secretion.[12] Yamamoto *et al.* have reported that acid suppression by omeprazole and cimetidine is dose-dependently accompanied with reduction of pepsin output in the rat stomach.[2] The present work shows that PGE_2 release was suppressed during drug dosing, and recovered to a level more than that in control wells by the 5th day after the end of dosing in both groups. This suggests that acid suppression results in a coordinated reduction in prostaglandin synthesizing capacity in the mucosa, but that this function quickly adapts to normal levels or higher promptly after the discontinuation of therapy. Therefore, post-dose effects in the gastric mucosa cannot be attributed to impaired prostaglandin release. Preliminary work from our laboratory has shown that PGE_2 release stimulated by histamine was significantly suppressed by the H_2-receptor antagonist cimetidine in both fundic and antral explants in the rabbit.[13] This suggests that the blockade of histamine H_2-receptor itself, in addition to the suppression of acid and pepsin output, may have contributed to the maximum decrease of PGE_2 secretion after 4 weeks in FAM-dosed group.

Ryberg *et al.* have demonstrated that gastric acid suppression for 28 days with ranitidine and omeprazole caused a significant increase in plasma gastrin concentration, and a consequent increase in the density of enterochromaffin-like (ECL) cells, histamine concentration and the histamine-producing enzyme, histidine decarboxylase (HDC) activity in the rat oxyntic mucosa.[14] In the present study, the hypergastrinaemia and the histamine released from ECL cells may have restored the

output of acid and pepsin to some extent, caused a gradual increase in total glycoprotein synthesis (i.e. ^{3}H-glucosamine incorporation) and sulphated glycoprotein synthesis during treatment in both groups. In fact, histological evaluation has shown that the vacuolar degeneration of parietal cells ((Figure 4), which is considered to reflect dilation of the secretory canaliculi[15]) is less remarkable after 4 weeks than 2 weeks in OME-treated group. The histological examination also showed that the volume of PAS-positive surface mucus after the 4-week treatments was similar to that seen in control tissues, whereas it was significantly reduced after only 2 weeks in both dosed groups (Figure 5).

In this study, glycoprotein sulphation was restored to control values or greater by the 5th day after the end of treatment, while ^{3}H-glucosamine incorporation was still suppressed in both groups. The proteolytic action of pepsin on gastric mucus is well known.[16] Mikuni-Takagaki & Hotta have shown that sulphated glycoproteins of gastric mucosa may inhibit peptic activity by binding the enzyme, but that non-sulphated glycoproteins do not exhibit the apparent pepsin binding and inhibitory activity (although they have a similar monosaccharide and amino acid composition to sulphated glycoproteins).[17] Moreover, they have reported that sulphated glycoproteins are intrinsically resistant to peptic digestion. Kim *et al.* have demonstrated that amylopectin sulphate, a synthetic sulphated polysaccharide, tends to bind to gastric mucin under conditions of low pH, and that the binding is reversible.[18] This may have led to the apparent discrepancy between ^{3}H- and ^{35}S- incorporation when the mucin was recovered in the presence of pepsin and acid 5 days after the end of drug exposure. Histologically, PAS-positive surface mucus production was not reduced at this time point in either of the treated groups.

There is a very small quantity of sialic acid in gastric mucus glycoprotein, which is one of five different monosaccharides constituting the carbohydrate side chains. However, sialic acid may play an important role in the defence of the stomach. It has been demonstrated by Slomiany *et al.* that the removal of peripheral fucose or N-acetylgalactosamine caused, in each case, only about a 5% reduction in glycoprotein viscosity, while an 18% drop in the viscosity occurred following the removal of sialic acid.[19] They also reported that removal of fucose or peripheral N- acetylgalactosamine increased the hydrogen ion retardation capacity of mucin by 7%, while a 28% increase was seen following the removal of sialic acid. Our present study shows that sialic acid content fell dramatically during and after dosing with omeprazole and famotidine, whereas there were only minor changes in the relative compositions of the neutral sugars. This result is similar to the findings of Vianello *et al.*[20] on gastric mucus after 6 weeks treatment with famotidine in duodenal ulcer patients. Furthermore, there is a clear association between hypochlorhydria and gastrointestinal infections.[21] Therefore, it may be suggested that terminal sialic acid residues on some sugar chains of the mucus glycoprotein are lost by the action of bacterial neuraminidases that may be elaborated in the gastric mucus under conditions of long-term suppression of acid.[22] Ohara *et al.* have shown that a single administration of high dose (200 μmol/kg) omeprazole caused a significant decrease (to 182% of control) of mucus glycoprotein, but did not change carbohydrate composition in the rat stomach.[23] Thus, long-term antisecretory therapy may have important influences on factors involved in gastric mucosal defence, and these should be considered in clinical trials that assess patients' response to drug treatment.

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