Upsala J Med Sci 97: 157–167

Effects of Omeprazole and Ranitidine on Plasma Gastrin Concentration and Stomach Gastrin Content in Rats

Rein Seensalu,[1] Kinfe Girma,[2] Bengt Romell[2] and Göran Nilsson[2]

[1]*Division of Gastroenterology & Hepatology, Department of Medicine and Department of Surgery and Research Center, Karolinska Institute, Huddinge University Hospital, Huddinge and* [2]*Department of Physiology, Faculty of Veterinary Medicine, University of Agricultural Sciences, Uppsala, Sweden*

ABSTRACT

Prolonged fasting and longer time between dosing and sampling reduced the plasma gastrin concentrations after omeprazole (80 μmol/kg x 2 for 14 days) treatment in male rats whereas the amounts of tissue gastrin were essentially unchanged during these initial experiments. After 28 days omeprazole (80 μmol/kg x 2) or ranitidine (375 μmol/kg x 4) that produced corresponding inhibition of acid secretion, increased the tissue gastrin content by 114 and 59 %. A low dose of omeprazole (20 μmol/kg x 2) also raised the gastric gastrin content (41 %), whereas no change was noted on treatment with a low dose of ranitidine (125 μmol x 4). Following recovery for 28 days no significant increases in gastrin were observed. 1, 3, 7, 14 or 28 days of treatment with omeprazole (80 μmol/kg x 2) gradually increased the gastric gastrin content beeing significantly raised already after 3 days. We conclude that a) measuring the tissue gastrin content may be the preferable method when changes in gastrin following long-term treatment with acid inhibiting drugs are to be determined, b) the amount of gastrin in the stomach increases rapidly following treatment with omeprazole and is approximately doubled following 28 days of treatment and c) after treatment for 28 days omeprazole was found to cause greater elevations in the tissue gastrin content than ranitidine despite similar degrees of basal acid inhibition.

INTRODUCTION

It is well known from animal and human studies that a reduction of the acid output will increase the plasma gastrin concentration (3, 6, 12, 14, 23). The elevated secretion of gastrin will exert a trophic effect on the acid-producing portion of the stomach (8, 14) and may also increase the number of fundic ECL (enterochromaffin-like) cells (10-11, 20-22, 27). In addition, long-term treatment with some acid-suppressing drugs has produced carcinoid (4, 5, 7, 19) or other (26) gastric tumours in rats. The occurrence of carcinoid tumours in rats following treatment with the selective H^+/K^+-ATPase inhibitor omeprazole has been ascribed to the elevated intragastric pH and the subsequent increase in gastrin release (4). However, the concept that an increased antral

pH during treatment with acid suppressing drugs is the only factor responsible for the gastrin increase is questioned by others (3, 16-18, 25). Thus, further studies are motivated on such drugs on gastrin production and release.

In the present investigation we have therefore studied the influence of the H_2-receptor antagonist ranitidine and omeprazole on tissue and plasma concentrations of gastrin, using doses of ranitidine and omeprazole that evoke similar degrees of inhibition of the basal acid output. Acid secretory experiments were performed in this study to confirm the inhibitory effects on acid secretion found in a previous investigation by us (24). In the present study we also investigated how low and high doses of omeprazole and ranitidine affect the tissue gastrin concentration following four weeks of treatment and four weeks of recovery from such treatment. We also determined how the gastric tissue concentration gradually changes during the treatment period with a high dose of omeprazole.

The effects of H_2-receptor antagonists (5, 10, 20-23, 27,) and omeprazole (2, 3, 8, 9-10, 20-23, 27) on gastrin concentrations in rats have been studied previously. In many of those studies gastrin concentrations in plasma and tissues were determined under different conditions, which complicates comparisons between the studies. To evaluate factors that are of importance in this context we have studied the influence on plasma and tissue gastrin concentrations during omeprazole treatment when the animals have free access to food and during different periods of food deprivation, as well as the effect of changing the interval between the last dose and sample collection.

MATERIALS AND METHODS

Animals

Male Sprague-Dawley rats, weighing 200-325 g were used in the acid secretory experiments. The rats were provided with a stainless steel cannula in the proximal part of the stomach under pentobarbitone anaesthesia. After surgery the rats were allowed to recover for three weeks before acid secretory experiments were started. Before each experiment the rats had free access to water but were fasting for 18-20 hours.

Male Sprague-Dawley rats weighing 170-200 g at the start of the experiments were used in the gastrin studies. The animals were weighed twice a week and the average weight gain was calculated. The rats, all of which had free access to water, were fed with standard rat food (R3, Ewos AB, Södertälje, Sweden) containing 22.0 % protein, 51.5 % carbonhydrate and 5.0 % fat, 13 MJ/kg. When fasting, rats had free access to water and were placed in mesh wire bottom cages 2 - 24 hours before they were killed.

Drugs and drug administration

The drugs omeprazole (generously supplied by AB Hässle, Sweden) and ranitidine (Glaxo Operations UK Ltd., England) were dispersed or dissolved in hydroxypropylmethylcellulose (Dow Corning Corp., Midland, USA). When hydroxypropylmethylcellulose (Methocel) was used as vehicel or in control experiments 2 mg/ml of $NaHCO_3$ was dissolved in 0.5% of Methocel and NaOH added in order to adjust pH to 9.0.

The omeprazole suspensions were kept in a refrigerator (+4°C) and renewed every 6th day. Fresh ranitidine solutions were prepared twice weekly to assure stability. On the basis of body weight determinations, the amounts of drugs to be administered were regularly adjusted. Drugs were given orally by gavage with a flexible plastic tube in volumes varying between 2.7 and 3.3 ml.

In all experiments the drugs or the vehicle were always administered twice (omeprazole at 7 am and 7 pm) or four (ranitidine at 1 am, 7 am, 1 pm and 7 pm) times daily in order to accomplish a persistent 24 hour inhibition during the treatment period. Samples from 9-10 rats were collected for each observation on gastrin concentrations.

Treatment of plasma and gastric tissue

After conclusion of the drug administration, rats were killed by decapitation. Blood was collected from the jugular and carotid vessels in heparinized glass tubes, cooled and centrifuged (5000 rpm) for 10 minutes at +4°C. The plasma was then frozen and stored at -20°C.

After bleeding, the abdominal wall was opened by a midline incision and the stomach was taken out. Blood vessels and mesenteric tissue along the major and minor curvatures were removed. The stomach was opened along the major curvature and gently rinsed with saline. Following determination of the weight the stomach was frozen on dry ice and then stored at -20°C until assayed for gastrin content by radioimmunoassay. The gastrin content of the whole stomach was determined. The stomach was homogenized and then boiled in water for 10 minutes (w/v=1/10). After cooling, the mixture was filtered through gauze and the filtrate was adjusted to 25 ml and then stored at -20°C.

Radioimmunological procedures

Gastrin was determined by radioimmunoassay according to a method described previously (15), using antibodies (4562) generously supplied by Professor Jens Rehfeld, Copenhagen, Denmark. Synthetic human gastrin 17 I (generously supplied by Dr J S Morley, ICI Ltd., England) was used as standard. Human gastrin I labelled with I^{125}, purchased from Milab, Malmö, Sweden, was used as tracer. Gastrin determinations were performed in duplicate and in serial dilutions. Plasma gastrin concentrations are expressed in pg/ml and the gastrin amounts in tissues in µg/stomach.

Acid secretion studies

Before acid secretory experiments the gastric cannula was opened and carefully rinsed to allow a free passage of gastric juice. Basal and pentagastrin (650 nmol/kg/h in s.c. infusion) stimulated gastric acid secretions were followed for 24 hours in rats given ranitidine (375 μmol/kg every sixth hour), omeprazole (80 μmol/kg every twelfth hour) or vehicle (3.0 ml, 2 or 4 times daily). On the seventh day, during ongoing drug administration, the acid secretion was determined in ranitidine treated rats hours 3,6,9,12,15,18,21 and 24 or during hours 4,8,12,16,20 and 24 in rats given omeprazole. Pentagastrin was given continously during the hours of sample collection. At collection of gastric juice the volume was measured and the acidity was determined by titration with 0.1 M NaOH to pH 7.0 using an automatic endpoint titrator system (Radiometer, Copenhagen, Denmark).

Gastrin studies

Before starting other studies, we determined how gastrin in plasma and stomach tissue were influenced by the conditions under which samples were collected. Thus we examined how feeding and food deprivation for various periods of time influenced the concentrations (series A). We also studied how variations in the interval between the last drug administration and sampling affected the gastrin concentrations (series B). The results from these initial studies were used in planning for more extensive studies in which the stomach gastrin content was determined after 4 weeks of treatment with omeprazole and ranitidine and following a subsequent recovery period of 4 weeks (series C). In series D we investigated how a high dose of omeprazole influences gastric gastrin content following 1, 3, 7, 14 and 28 days of administration.

Statistical evaluations

All values are expressed as mean ± SEM. Statistical evaluation of the results in series A and B was carried out by regression analysis. In series C analysis of variance and Bonferroni's test was carried out for multipel comparisons and in series D Student's t-test was used for comparisons between groups.

RESULTS

Ranitidine (375 μmol/kg x 4) inhibited the 24 hour basal and pentagastrin stimulated acid secretions with 82±2% (mean±SEM) and 79±1% (fig.1a). The corresponding inhibition for omeprazole (80 μmol/kg x 2) was 80±5% and 78±2% (fig. 1b).

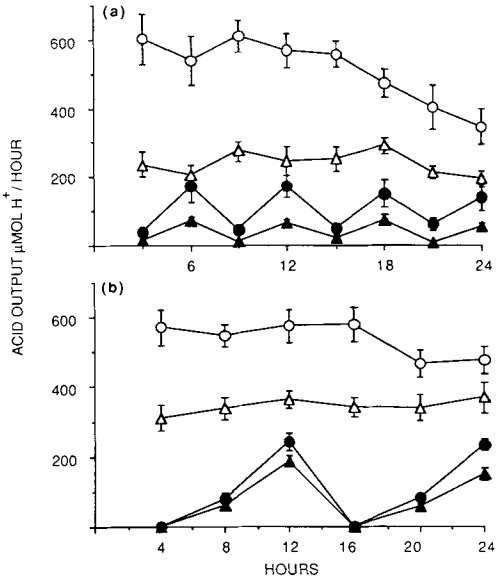

Fig. 1.

Basal (▲ △) and pentagastrin stimulated (● ○) acid out-put during 24 hours in gastric fistula rats (n 6-10) during the seventh day of administration of a) 375 µmol/kg (▲●) ranitidine or 3.0 ml of Methocel (△ ○) at hours 0, 6, 12 and 24 or during administration of b) 80 µmol/kg of omeprazole (▲ ●) or 3.0 ml of Methocel (△○) at hours 0 and 12. Gastric juice were collected at hours 3,6,9,12,15,18,21,24 (ranitidine) or 4,8,12,16,20, 24 (omeprazole).

No significant differences in body or stomach weights were seen between the different treatment groups in series A - C (results not illustrated). In series A rats were given omeprazole (80 µmol/kg x 2) for 14 days and were killed 12 hours after the last dose of omeprazole. The animals had access to food until killed (0) or they had been fasting for 2, 6, 12 or 24 hours. As can be seen in Fig. 2a, plasma gastrin concentrations gradually and significantly decreased as the period of fasting was prolonged ($t=-7.29$, $p\leq0.001$), whereas the amounts in gastric tissue (Fig. 2b) at the corresponding points of time were essentially unchanged ($t=1.65$, NS). The rats in series B had free access to food and the concentration of gastrin in plasma was significantly ($t=-5.29$, $p\leq0.001$) lowered as time between dosing and sampling was prolonged (Fig. 3a). The amounts of gastrin in the stomach were not greatly influenced ($t=1.75$, NS), although some increase of gastrin content was seen as the period between sampling and last administration of the drug was increased (Fig. 3b). The time point 0 hour after drug administration was omitted in the statistical analysis. The rationale for that is that the time between administration and sampling of plasma and stomach tissue was too short to allow omeprazole to interfere with acid and gastrin secretion.

Effects of treatment with omeprazole (20 or 80 µmol/kg x 2) or ranitidine (125 or 375 µmol/kg x 4) for 28 days and following 28 days of recovery were studied in series C. After 18-20 hours of fasting the treated animals were killed 6 (ranitidine) or 12 (omeprazole) hours after the last dose. The high dose of omeprazole (Fig. 4) and ranitidine (Fig. 5) significantly increased the tissue content of gastrin. The largest amounts were found when animals were given the high omeprazole dose for four weeks. However, the high dose of ranitidine caused a gastrin increase that was closer to that produced by the low dose of omeprazole.

No change in tissue gastrin content was noted in rats treated with the low dose of ranitidine (Fig. 5). After 4 weeks of recovery, the amounts of tissue gastrin in omeprazole treated rats were somewhat, but not significantly, raised whereas the amounts in ranitidine-treated rats were unchanged when compared to the recovery controls.

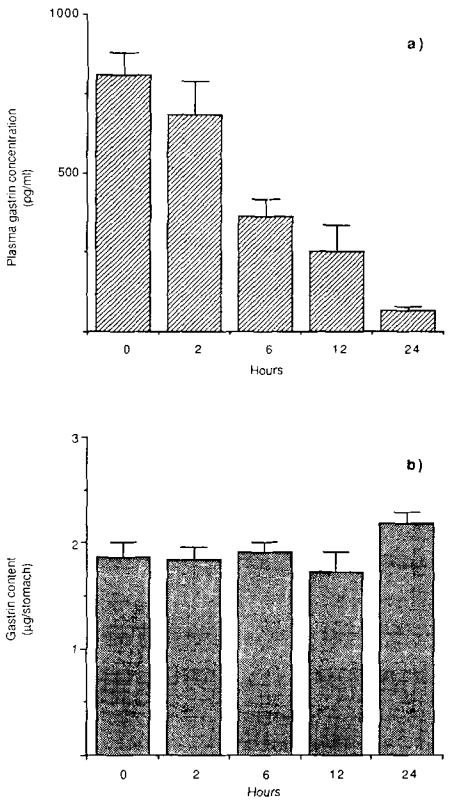

Fig 2.
(a) Plasma gastrin concentration and (b) gastric gastrin content, expressed as mean ± SEM, in rats treated with omeprazole 80 µmol/kg twice daily for 14 days. The rats (n=9-10) were killed after having free access to food (0 hour) or after 2, 6, 12 or 24 hours of food deprivation.

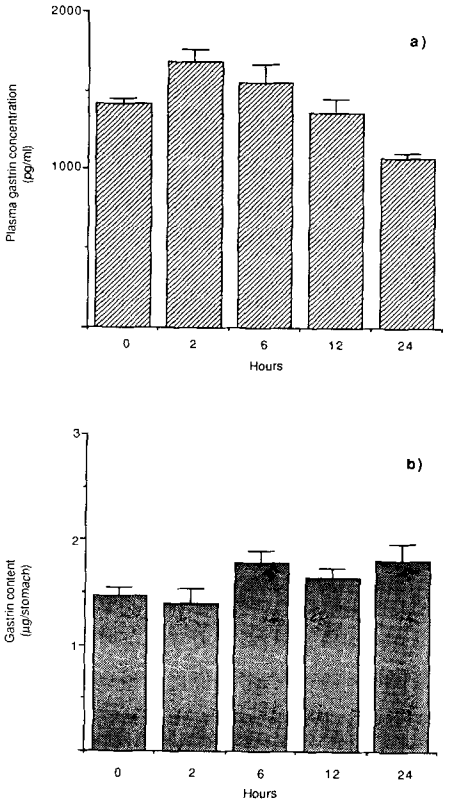

Fig 3.
(a) Plasma gastrin concentration and (b) gastric gastrin content in rats having free access to food (n=9-10) treated with omeprazole 80 µmol/kg twice daily for 14 days and killed 0,2,6,12 or 24 hours after the administration of the last dose. Results are expressed as mean ± SEM.

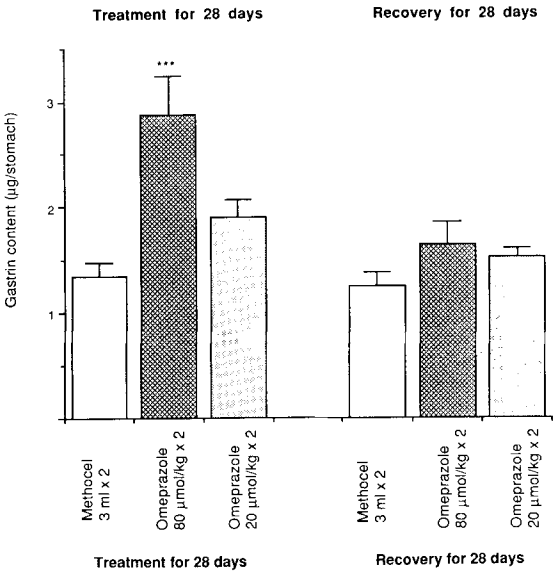

Fig 4.
Stomach gastrin content in rats (n=10) treated with 20 or 80 µmol/kg of omeprazole or with 3 ml of Methocel every twelfth hour for 28 days and following recovery for 28 days. The results are expressed as mean ± SEM. *** indicates significant ($p \leq 0.001$) difference between Methocel and omeprazole-treated rats. Bonferroni's test.

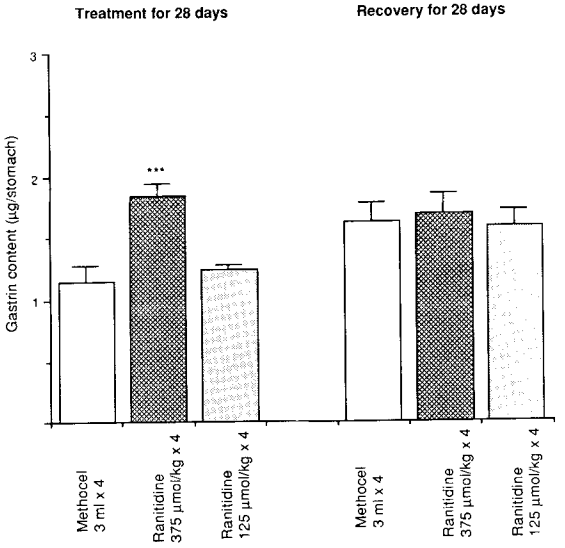

Fig 5.
Stomach gastrin content in rats (n=10) treated with 125 or 375 µmol/kg of ranitidine or with 3 ml of Methocel every sixth hour for 28 days and following recovery for 28 days. *** indicates significant ($p \leq 0.001$) difference between Methocel and ranitidine-treated rats. Bonferroni's test.

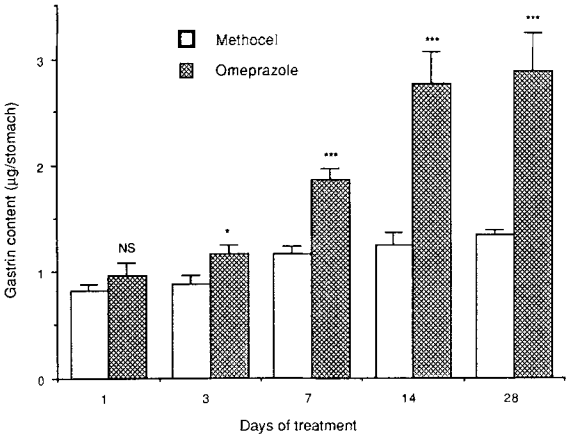

Fig.6.
Increase in stomach gastrin content in rats (n=7-10) treated with 80 µmol/kg of omeprazole or with 3 ml of Methocel every twelfth hour for 1, 3, 7, 14 or 28 days. * ($p \leq 0.05$) and *** ($p \leq 0.001$) indicate significant differences between Methocel and omeprazole-treated rats after 3 and 7 - 28 days of treatment respectively. Student's t-test.

The results from series D are illustrated in Fig. 6. The amounts of gastrin gradually increased and were 31 per cent larger after 3 days ($p \leq 0.05$), which can be compared to the increase of 114 per cent ($p \leq 0.001$) following 28 days of treatment. It should be noted that the gastrin values following 28 days of treatment are the same as in series C.

DISCUSSION

In the present study attempts were made to evaluate how duration of fasting or variation of the time period between last drug administration and sampling influence gastrin in plasma and tissue. It is previously known that deprivation of food in rats decreases the plasma and antral gastrin concentrations (13). Recently Wu et al (28) demonstrated a time dependent decrease in tissue gastrin concentration and antral messenger RNA(mRNA) level in starving untreated rats. A significant decrease of both antral gastrin and gastrin mRNA concentration occurred already after 12 hours´ starvation. In the present study we have demonstrated that fasting for 2 - 24 hours following 14 days of treatment with omeprazole gradually and considerably (92% after 24 hours) reduces the plasma gastrin concentrations, whereas the amounts of antral gastrin measured at corresponding times are essentially unchanged. It seems reasonable to assume that a prolonged administration of omeprazole to rats causes an increase of tissue gastrin concentration that may be relatively less sensitive to alterations in the feeding state. When the dosing intervals were varied and the animals had free access to food plasma gastrin levels remained more stable. Some increase in plasma gastrin concentration was seen when omeprazole exerted its optimal effect (after 2-6 hours), whereas concentrations gradually and significantly decreased as the period between sampling and the last administration of the drug was increased. The above results underline the importance of well established sampling routines for the collection of plasma and gastric tissues for gastrin determination. The lack of such routines will contribute to extensive variations in results in individual studies and great difficulties in comparing results from different laboratories. Taken together, the results of this methodological part of the study suggest that, when long-term effects on gastrin changes are studied results from determinations of tissue gastrin concentrations seem to be relatively independent of temporary variations in degrees of food stimulation, intragastric pH changes and other factors that may influence gastrin release.

In a previous study of ours (24) we gave rats various doses of omeprazole and ranitidine and determined the effects on acid secretion. In the present study we have confirmed some of the results on acid secretion from that study and we have selected doses of omeprazole and ranitidine that caused comparable inhibitions of the basal acid output. When these doses were administered twice (omeprazole) or four (ranitidine) times per day during 28 days the stomach gastrin content of the omeprazole-treated rats reached higher values than that in the ranitidine treated animals. Larsson (11) and Ryberg (23) and their coworkers concluded that when acid secretion is inhibited to a similar degree, ranitidine is capable of inducing hypergastrinemia of the same magnitude as omeprazole. Therefore in their view a direct action on the gastrin cells by either of the two

compounds seems less probable. However, in another study of the same group (22) previously used doses of omeprazole and ranitidine (23) failed to cause a corresponding degree of acid inhibition. Our studies of gastrin in the stomach and plasma (24) following treatment with omeprazole and ranitidine indicate larger increases in gastrin levels following omeprazole treatment. Therefore we cannot exclude the possibility that omeprazole or ranitidine may influence the ability of the gastrin cells to secrete gastrin by other mechanisms than by affecting the intraluminar pH of the stomach. Such a concept is supported by results from Ohe et al (16-18) who studied gastrin release in perfused rat stomachs and by results from Decktor et al (3) and Simoens et al (25) in studies on gastric fistula rats and dogs.

When omeprazole (80 μmol/kg) was given twice daily for various periods of time the amounts of gastric gastrin gradually increased and following 4 weeks of treatment they were 114 per cent above the control level. A slight but insignificant increase in tissue gastrin content was seen already after one day of omeprazole administration whereas administration for 3 days caused a marked and significant increase. These findings are in agreement with the results of Brand and Stone (1) who studied the time course of stimulation of gastrin secretion and synthesis in rats after intraperitoneal administration of omeprazole. They found that antral gastrin mRNA levels were significantly increased after 2 days (but not after one day) of omeprazole administration.

Following four weeks of recovery from omeprazole treatment, the amounts of gastric gastrin were slightly and insignificantly increased whether the rats had been treated with the high or the low dose of omeprazole. A similar tendency was found in studies presented by Creutzfeld et al (2) and Larsson et al (9) following 42 (2) and 35, but not 70 (9), days of recovery after omeprazole treatment. However, since the doses of omeprazole, length of omeprazole treatment, number of administrations per day and routines for collection of blood samples differed between these studies, no direct comparisons can be made. No sustained elevations of the gastrin concentrations were found after 4 weeks in rats treated with ranitidine when compared with the vehicle treated recovery controls. It should be noted that the gastrin contents in control rats treated with the vehicle four times per day were somewhat higher than in recovery controls treated twice per day. No certain explantion can be given to this difference.

In summary, the present results indicate the importance of controlled experimental conditions in studies of gastrin in plasma and gastric tissue. In studies of long-term effects on the gastrin mechanism determinations of tissue concentration may offer more stable and less time dependent results. During omeprazole treatment increased amounts of gastrin were found in gastric tissue already following 3 days of treatment and they gradually increased thereafter. Following 28 days of treatment, omeprazole produced higher tissue amounts of gastrin than ranitidine at doses selected to cause similar inhibition of gastric secretion.

ACKNOWLEDGMENTS

The authors wish to express their gratitude to Mrs Annika Wagman and Mrs Elisabeth Dugner for their technical assistance and to Mrs Margareta Topel and Ms Catrine Olsson for typing the manuscript. This investigation was supported by grants from the Swedish Medical Research Council (04X-3521), the Swedish Society of Medicine and "Förenade Liv" Mutual Group Life Insurance Company, Stockholm, Sweden.

REFERENCES

1. Brand, S. & Stone, D: Reciprocal regulation of antral gastrin and somatostatin gene expression by omeprazole-induced achlorhydria. J Clin Invest 82: 1059-1066, 1988.
2. Creutzfeldt, W., Stöckman F., Conlon J.M., Fölsch U.R., Bonatz G &Wülfrath M: Effect of short- and long-term feeding of omeprazole on rat gastric endocrine cells. Digestion 35 (suppl 1): 84-97 1986.
3. Decktor, D.L., Pendelton R.G., Kellner A.T & Davis M.A: Acute effects of ranitidine, famotidine and omeprazole on plasma gastrin in the rat. J Pharmacol Exp Ther 249: 1-5, 1989.
4. Ekman, L., Hansson E., Havu N., Carlsson E & Lundberg C: Toxicological studies on omeprazole. Scand J Gastroenterol 20 (suppl 108): 53-69, 1985.
5. Harleman, J.H., Betton G.R., Domer C.S & McCrossan M: Gastric neutoendocrine cell hyperplasi after treatment with the long-acting potent H2-receptor antagonist SK&F 93479, Scand J Gastroenterol 22, 595-600, 1987.
6. Halter, F., Witzel L., Häcki W.H., Olah A.J., Heitz P & Varga L: Gastric secretion, the parietal cell and gastrin response to histamine H2-receptor antagonists in the rat. In: Cimetidine. Proceedings of an International Symposium on Histamine H2-receptor antagonists, (ed.W. Creutzfeldt), pp. 108-113, 1978, Excerpta Medica, Amsterdam.
7. Hirth, R.S., Evans L.D., Burober R.A & Olesen F.B: Gastric entero-chromaffin-like cells hyperplasia and neoplasia in the rat: an indirect effect of the histamine H2-receptor antagonist, BL - 6341. Toxicol Pathol 16: 273-287, 1988.
8. Håkansson, R., Blom H., Carlsson E., Larsson H., Ryberg B & Sundler F: Hypergastrinaemia produces trophic effects in stomach but not in pancreas and intestines, Regul Pept 13, 225-233, 1986.
9. Larsson, H., Carlsson E., Håkansson R., Mattson H., Nilsson G., Seensalu R., Wallmark B & Sundler F: Time-course of development and reversal of gastric endocrine cell hyperplasia after inhibition of acid secretion. Gastroenterology 95: 1477-2486, 1988.
10. Larsson, H., Carlsson E., Mattson H., Lundell L., Sundler F., Sundell G.,Wallmark B., Watanabe T & Håkansson R: Plasma gastrin and gastric enterochromaffinelike cell activation and proliferation. Studies with omeprazole and ranitidine in intact and antrectomized rats. Gastroenterology 90: 391-399, 1986.
11. Larsson, H., Håkansson R., Mattson H., Ryberg B., Sundler F & Carlsson E: Omeprazole: Its influence on gastric acid secretion, gastrin and ECL cells. Toxicol Pathol 2: 267-272, 1988.
12. Lanzon-Miller, S., Pounder R.E., Chronos N.A.F., Raymond F., Hamilton M.R & Dagleish D: Twenty four hour intragastric acidity and plasma gastrin concentration in healthy colunteers taking nizatidine 150 mg, nizatidine 300 mg, ranitidine 300 mg, or placebo at 21 00 h, Gut 29, 1364-1369, 1985.
13. Lichtenberger, L.M., Lechago J & Johnson L.R: Depression of antral and serum gastrin concentration by food deprivation in the rat, Gastroenterology 68, 1473-1479, 1975.
14. Mazzacca, G., Cascione F., Budillon G., D'Agostino L., Ciminom L & Femiano C: Parietal cell hyperplasia induced by long-term administration of antacids to rats. Gut 19: 798-801, 1978.
15. Nilsson, G: Increased plasma gastrin levels in connection with inhibition of gastric acid responses to sham feeding following bulbar perfusion with acid in dogs. Scand J Gastroenterol 10: 273-277, 1975.

16. Ohe, K., Nakamura M., Fujiwara T., Matsumoto H., Kohchi M & Miyoshi A: Effect of H_2-receptor antagonists, cimetidine and YM-11170, on serum gastrin levels in lumen-perfused rats. Dig Dis Sci 11: 981-989, 1983.
17. Ohe, K., Yagita M., Miura Y., Nagamatsu Y & Taoka Y: Comparison of the effect of H2-receptor anatgonists and omeprazole on serum gastrin levels in lumen perfused rats. Dig Dis Sci 31 (suppl 10): 494S, 1986.
18. Ohe, K., Yagita M., Yoshikawa I., Nagamatsu Y., Miura Y & Taoka Y: Mechanism of increase in serum gastrin levels by H2-receptor antagonists and omeprazole in lumen-perfused rats. Gastroenterology 96: A 374, 1989.
19. Poynter, D., Pick C.R., Harcourt R.A., Selway S.A.M., Ainge G., Harman I.W., Spurling N.W., Fluck P.A & Cook J.L: Association of long lasting unsurmounmtable histamine H2-blockade and gastric carcinoid tumours in the rat, Gut 26, 1284-1295, 1985.
20. Ryberg, B, Tielemans Y, Axelson J, Carlsson E, Håkanson R, Mattsson H, Sundler F & Willems G: Gastrin stimulates the self-replication rate of enterochromaffinlike cells in the rat stomach. Effects of omeprazole, ranitidine, and gastrin-17 in intact and antrectomized rats. Gastroenterology 99: 935-42, 1990.
21. Ryberg, B, Tielemans Y, Axelson J, Carlsson E, Håkanson R & Mattsson H: Thropic effects of continous infusion of LEO^{15}-gastrin-17 in the rat. Gastroenterology 98: 33-38, 1990.
22. Ryberg, B., Bishop A.E., Bloom S.R., Carlsson E., Håkansson R., Larsson H., Mattsson H., Polak J.M & Sundler F: Omeprazole and ranitidine, antisecretagogues with different modes of action, are equally effective in causing hyperplasia of enterochromaffin-like cells in rat stomach. Regul Pept 25: 235-246, 1989.
23. Ryberg, B., Mattsson H., Larsson H & Carlsson E: Correlation between inhibition of gastric acid secretion, plasma gastrin, and oxyntic mucosal histidine decarboxylase activity in the rat. Scand. J. Gastroenterol. 24: 287-292, 1989.
24. Seensalu, R., Girma K., Romell B & Nilsson G: Time-course of inhibition of gastric acid secretion in gastric fistula rats by omeprazole and ranitidine, Eur J Pharmacol 180, 145-152, 1990.
25. Simoens, C., Woussen-Colle M.C & De Graef J: Effects of acute suppression of acid secretion by omeprazole on postprandial gastrin release in conscious dogs. Gastroenterology 97: 837-845, 1989
26. Streett, C.S., Cimprich R.E & Robertson J.L: Pathologic findings in the stomachs of rats treated with the H2-receptor antagonist tiotidine. Scand. J. Gastroenterol 19 (suppl 101): 109-117, 1984.
27. Tielemans, Y., Håkansson R., Sundler F & Willems G: Proliferation of enterochromaffinelike cells in omeprazole-treated hypergastrinemic rats. Gastroenterology 96: 723-729, 1989.
28. Wu, V, Sumii K, Tari A, Sumii &, Walsh J: Regulation of rat antral gastrin and somatostatin gene expression during stravation and after refeeding. Gastroenterology 101: 1552-1558, 1991.

Address for reprints:

Dr Rein Seensalu
Division of gastroenterology & hepatology
Department of Medicine, K63
Huddinge University Hospital
S-141 86 Huddinge Sweden