Effect of Long Acting Somatostatin Analogue, Octreotide (SMS 201-995) on Omeprazole-Induced Hypergastrinemia in Human

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Özet: *UZUN ETKİLİ SOMATOSTATİN ANALOĞU OCTREOTİD'İN (SMS 201–995) İNSANLARDA OMERAZOLA BAĞLI HİPERGASTRİNEMİ ÜZERİNE ETKİSİ*

İnsanlarda ve hayvanlarda asit sekresyonunun ilaçlarla inhibisyonu serum gastrin seviyelerini artırmaktadır. Omeprazolde serum gastrin seviyelerini yükselten uyaranlardan biridir. Biz bu çalışmada omeprazol tedavisi sonrası meydana gelen gastrinemiye bağlı trofik etkilerin uzun etkili somatostatin anoloğu olan SMS 201-995 octreotide ile antagonize edilip edilemeyeceğini araştırdık.

20 gönüllü bu çalışmaya alındı. 20 mg 5 gün boyunca omeprazol verilen gönüllülerin yarısına 3 gün SMS 100 μ g diğer yarısına saline günde 3 kez subcutan 2 gün uygulandı ve gastrin seviyeleri sabah 9'da ratioimmunassay (RİA) ile ölçüldü.

Omeprazol anti SMS grubu ile omeprazol + saline grubunun bazal gastrin seviyeleri sırasıyla 20.71 ± 46 ve 20.65 ± 2.9'da ve aralarında istatistiksel bir farklılık yoktu. Omeprazol uygulamasından sonra her iki grupta da gastrin seviyeleri ilk 3 gün artarak 22.84 ± 3.6; 23.09 ± 4; 23.85 ± 3.5 ve 21.34 ± 3.9; 22.94 ± 1.8; 24 ± 3.6'ya yükseldi. Her iki gruptada oluşan artış birbirine paraleldi ve aralarında fark yoktu. Fakat 3. gün her iki grubun gastrin düzeyleri bazal seviyelerinden anlamlı ölçüde yüksekti (p<0.05). 3. gün uygulanan SMS gastrin seviyelerinde azalma yaparak 4. gün gastrin seviyelerini 18.91 ± 2.27'ye çekti ve bazal değerin altına inmesine neden oldu. Saline uygulanan grupta ise 4. gün gastrin seviyelerinde artış devam etti (25.35 ± 2.3). Bu grubun gastrin seviyeleri 1-4. günler arasında sırasıyla bazal değere göre %3.34, %11.08, %16.22 (p<0.05) ve %22.76 (p<0.01) oranında fazlaydı.

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Summary: *Drug-induced inhibition of acid secretion produces increased serum gastrin levels in animals and humans. Omeprazole also produced serum gastrin elevation in rats. Therefore, we investigated whether long acting somatostatin analogue (SMS 201-995 octreotide) could antagonize the trophic effect induced by hypergastrinemia resulting from omeprazole treatment.*

Twenty healthy volumteers participated to this study. The subjects have received omeprazole 20 mg for 5 on the days. Third day of receiving omeprazole, SMS 201-995 100 μg (n : 10) or saline (n : 10) perfused tree times a day by subcutaneously (sc) with same procedure for one day. Serum gastrin level was measured by radioimmunoassay (RIA) at 9 am for 5 days belong. Mean basal serum gastrin levels were 20.71 ± 4.6 pg/ml in omeprazole plus SMS 201-995 and 20.65 ± 2.9 pg/ml in omeprazole plus saline groups. This difference was not significant statistically. After administration of omeprazole, gastrin levels increased by linearly, mean gastrin levels were 22.84 ± 3.63, 23.09 ± 4.03 and 23.85 ± 3.52 pg/ml in omeprazole plus SMS 201-995, 21.34 ± 3.99, 22.94 ± 1.83, and 24.00 ± 3.66 pg/ml in omeprazole plus saline group in 1-3 days respectively. This increasing of serum gastrin levels in both groups was parrellel and no significant different statistically compared to each other. But gastrin levels of both groups in the third day were significantly higher than those of the baseline (p<0.05). In the fourth day, gastrin levels were significantly reduced to under the baseline by administration of SMS 201-995 in third day. In this group mean gastrin gastrin level of the omeprazol plus saline group decreased from 20.71 ± 4.64 pg/ml to 18.91 ± 2.27 pg/ml (8.60%) compared to baseline, this difference was not significant. Level never reduced and continoued to increase (25.35 ± 2.3) at the fourth day. In this group gastrin level were higher 3.34%, 11.08%, 16.22% (p<0.05) and 22.76% (p<0.01) than the baseline in 1-4 days repectively. In addition, gastrin level of omerprazol plus SMS group were significantly lower than that of omeprazol plus

Ayrıca ilave olarak 4. gün omeprazol + SMS grubunun gastrin seviyeleri omeprazol + saline grubuna göre anlamlı ölçüde azalmıştı ($p<0.01$).
Bu sonuçlar SMS 201 uygulamanın omeprazolun oluşturduğu hipergastrinemiyi tamamen önlediğini göstermektedir.

Anahtar kelimeler: Somatostatin, omeprazole, gastrin, human.

saline group in fourth day ($p<0.05$).
These results shown that administration of SMS 201-995 was totally abolished omeprazole-induced hypergastrinemia.

Key words: Somatostatin, omeprazole, gastrin, human.

Drug-induced inhibition of acid secretion produces increased serum gastrin levels in animals and humans. This is independent of inhibitory type since histamine H_2-receptor antagonists (1-5) H^+ / K^+ -ATPase inhibitors (1, 4, 6) and phenoxyisobetyrate derivatives (7) have all been associated with hypergastrinaemia. In animals, administration of H_2-antagonists, whether short acting such as cimetidine (3), ranitidine (5, 11) or oxmetidine (1) or long–acting such as loxtidine (2) have resulted in hypergastinaemia. Similarly, treatment with substituted benzimidazoles such as omeprazole (1,4,5) also produced serum gastrin elevation in rats.

In general, the magnitude of gastrin increase is correlated with the degree and duration of acid inhibition induced by the antisecretory medication. It was reported that a dose relationship between the level of omeprazole induced acid inhibition and fasting gastrin concentration (8). However, greater that 80% inhibition of peak acid output had to be obtained before fasting gastrin was significantly increased in humans treated for five days with varying omeprazole doses (9).

In humans, H_2-antagonist therapy has usually resulted in an increase in plasma gastrin, which was felt to be caused by drug-induced suppression of acid secretion (10). When ranitidine 150 mg bid was compared to omeprazole 20 mg in the morning duodenal ulcer patients during a 28-day treatment period, both drugs produced a significant increase of, plasma gastrin associated with each regimen returned to normal two weeks after discontinuation of medication (11,12). There was a significant inverse correlation between 24-hour integrated intragastric acidity and plasma gastrin levels (12). The plasma gastrin increments associated with either drug treatment were significatly lower than those observed in pernicious anaemia patient evaluated under similar study conditions (13).

Gastrin release is stimulated by peptides, amino acids and calcium in the gastric lumen, by activation of nervous reflexes, by bombesin-like peptides and by circulating catecholamines (14,15). Gastrin release is inhibited by low gastric luminal pH, by several gastrointestinal peptides such as somatostatin and by specific prostaglandins (14,15).

Acidifying intragastric pH to less than 3 inhibts gastrin release in response to a meal, since intragastric pH usually falls to between 2 and 3 after eating. Maintaining an intragastric pH of greater that 3 in the presence of luminal protein or amino acids, does not produce increased gastrin relese (14,15). Chronic achlorhydria, as occurs in patients with pernicious anaemia, is associated with elevated serum gastrin levels. In humans serum gastrin has been shown to increase after a minimum of five hours of gastric alkalinization with sodium bicarbonat (17). However, gastrin release following a similar period of neutralization could not be confirmed in a subsequent study (18).

The presence of this negative-feedback loop, in which gastrin-stimulated acid secretion produces an inhibition of further gastrin release from the antral mucosa, has led to a classification of hypergastrinemia based on whether of increased (19). Pathological hypergastrinemia, ie. associed with acid hypersecretion, is caused by gastrin-secreting tumours (Zollinger-Ellison syndrome), antral gastrin cell hyperfunction, isolated retained antrum or pheochromocytoma. Appropriate hypergastrinemia, ie. with low or absent acid secretion, occurs with atrophic gastritis sparing the antrum, postvagotomy, in renal failure and

Table I : Mean Gastrin Levels (pg/ml) in The Groups and Statisticaly Comparison

Groups	Baseline	Days 1	2	3	4
Om - SBS	20.71 ± 4.6	22.84 ± 3.6	23.09 ± 4.0	23.85 ± 3.5*	18.91 ± 2.2
Om - Saline	20.65 ± 2.9	21.34 ± 3.9	22.94 ± 1.8	24.00 ± 3.6*	25.35 ± 2.3**
p	—	—	—	—	<0.01

* : Differene from baseline p<0.05.
** : Difference from baseline p<0.01.

with antisecretory medications (19).

Somatostatin (SMS) has powerful inhibitory effects on different gastric function (20). It supresses acid and pepsin secretion anal inhibits gastrin release acid and pepsin secretion anal inhibits gastrin release in normal subjects after a standard meal and in patients with gastrinoma (21).

From attempts to derive an analoque of SMS that would be better suited for clinical use, several potent and long-acting synthetic peptides have been developed (22,23). One analoque is SMS 201-995. This octapeptide is 20 to 40 times more potent that SMS, and is more selective in the inhibition of growth hormon than the naturally occuring peptide (24). This drug is stable to enzyme degradation and may therefore be administered by intravenous bolus or subcutaneously. Given intravenously, its elimination half-life is 41-58 min; administered subcutaneously its elimination half-life is 113 to 120 min (24).

To stimulating replication of G cells and ECL-cells with omeprazole has been reported to reduce D-cell number and thereby decrease SMS production by the gastric antrum. Somatostatin displays antiproliferative activity and normally functions as an inhibitor of gastrin release. Consistent with these actions, administration of a somatostatin analogue was found to partially reverse the trophic effects of omeprazole on the rat stomach (25).

We investigated the effect of subcutaneous injection of SMS 201-995 on serum gastrin levels with receiving omeprazole. Therefore, we will investigate whether a long acting somatostatin analoque (SMS 201-995) could inhibit hypergastrinemia resulting from omeprazole treatment.

MATERIAL AND METHODS

Twenty volunteers agreed to participate to the study after the protocol and the test procedures has ben explained them. All of the subjects completed protocol. Their age range were (20±2) years. Subjects had no history of smoking, or of taking non-steroidas anti-inflammatory analgesics, or anti-secretory use. They ingested no medication for at least 15 days perior to enrollment in the study. Before entrance in the study, each individual had a medical history taken and physical examination performed. All had normal biochemical and hematological values. Esophago-gastroduodenoscopy have performed to each participant. Using an Olympus GIF K–20 gastroscop (Olympus Co. of JAPAN) and hypopharyngeal anesthetic have performed by lidocain. Intravenous diazem have given as necessary for sedation. Peptic ulcer of gastritis were excluded by endoscopy.

The subjects have received omeprazole 20 mg (n : 20) (Astra-Sweden) for five days in the morning 30 min. before breakfast.

Third day of receiving omeprazole, SMS 201-995 mg or saline (SF) perfused tree times a day subcutaneously for one day.

Serum was sampled for gastrin determination before receiving omeprazole for baseline level. Serum gastrin was determined every day for five days.

Gastrin was measured by radioimmuno assay (Becton-Dickinson Immunodiagmastics, Sensitivity of the assay is 10 pg/ml of serum. The interassay coefficient of variation is 10%, and the intra-assay coefficient of variation 5%.

Results are reported as the mean. Changes from

base line were determined with wilcoxon signed rank test and means of diffenetions of two groups were with Mann Whithney-U test.

RESULTS

Mean basal serum gastrin levels were 20.71 ± 4.6 pg/ml in omeprazole plus SMS 201-995 and 20.65 ± 2.9 pg/ml in omeprazole plus saline groups. This difference was not significant statistically. After administration of omeprazole, gastrin levels increased by linearly, mean gastrin levels were 22.84 ± 3.63, 23.09 ± 4.03 and 23.85 ± 3.52 pg/ml in omeprazole plus SMS 201-995, 21.34 ± 3.99, 22.94 ± 1.83, and 24.00 ± 3.66 pg/ml in omeprazole plus saline group in 1-3 days respectively. In both groups increasing of serum gastrin levels was parellel and no significant different statistically compared to each other. Gastrin levels were significantly reduced to under the baseline by administration of SMS 201-995 In third day. In this group mean gastrin level decreased from 20.71 ± 4.64 pg/ml to 18.91 ± 2.27 pg/ml (8.60%) compared to baseline, this difference was not significant. Level never reduced and continued to increase (25.35 ± 2.3) at the fourth day. In this group gastrin level were higher 3.34%, 11.08%, 16.22% ($p<0.05$) and 22.76% ($p<0.05$) than the baseline in 1-4 days repectively in addition gastrin levels of omerprazole plus SMS group were significantly lower than those of omeprazole plus saline group fourth day.

DISCUSSION

The significant stimulatory effect of omeprazole on human serum gastrin level, demonstrated in the present study is apparently is agrement with previous observation. Also this study demonstrated that administration of SMS 201-995 totally abolished omeprazole-induced hypergastrinoma. At present no study addressed directly the effect of SMS 201-995 in human about this subject.

In studies, the inhibitory action of SMS 201-995 on hypergastrinemia has been attributed to supressions of stimulated of gastrin.

Several animal and human studies suggested that neither H_2-receptor antagonists nor substituted benzimidazoles stimulated gastrin release directly, but, instead, acted indirectly through inhibition of acid secretion. This effect on gastrin release

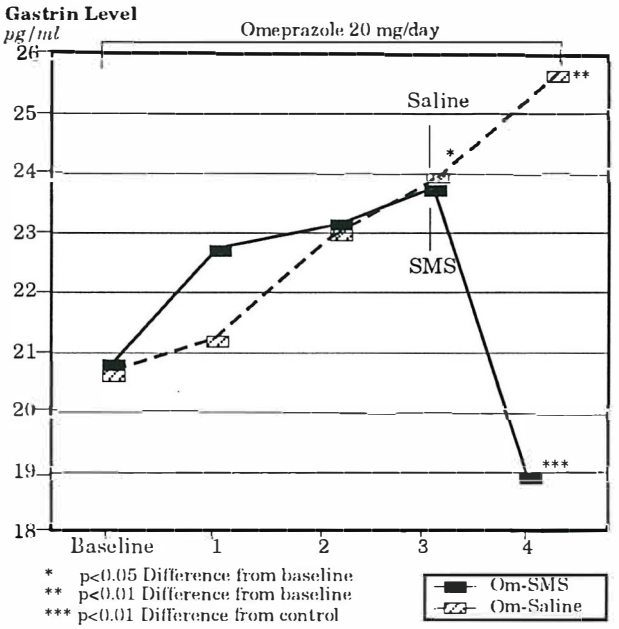

Figure 1 : After administration of ameprazole, gastrin levels increased by linearly, this increasing of serum gastrin levels in both groups was parrellel and no signigficant different statistically compared to each other. But gastrin levels of both groups in the third day were significantly higher than those of the baseline. In the fourth day, gastrin levels were significantly reduced to under the baseline by administration of SMS 201-995 in third day. In addition, gastrin level of omerprazol plus SMS group were significantly lower than that of omeprazol plus saline group in fourth day.

may be especially amplified after a meal, when pH would remain elevated following antisecretory therapy, rather than falling to a pH of 2 to 3 without drug administration (15,16). In fasted rats, plasma gastrin levels doubled after omeprazole, 10 μmol/kg intramuscularly, and an intragastric water infusion. An intragastric infusion of 0.15 M hydrochloric acid following the same omeprazole dose abolished the gastrin increment (26).

In dogs, postprandial gastrin levels rose by a similar amount after either intragastric titration to pH 6.4 alone, or with intragastric titration combined with cimetidine 2.5 mg / kg / h, ranitidine 0.5 mg / kg / h or omeprazole 2 mg / kg (27). Other studies in dogs have shown that the meal stimulated gastrin release observed at pH 5.5 following antisecretory medication such as omeprazole could be entirely abolished by maintaining intragastric pH at 2.5 (28).

In humans, several studies have failed to demonstrate a significant effect of H_2-receptor antag-

onists on postprandial gastrin release if intragastric pH was maintained at pH 5.0 or greater (29,30). Similarly, omeprazole had no direct affect on postprandial gastrin levels if intragastric pH was maintained at pH 5.5 (31) further, during a four-week treatment period of omeprazole 10 mg, 20 mg or 40 mg in the morning, or ranitidine 150 mg bid, mealstimulated gastrin response remained higher in response to an intragastric pH of 5.5 than pH 2.5 (11), suggesting that the normal negative feedback inhibition of gastrin release mediated by intragastric acidity 16 was not altered by omeprazole or H_2-antagonist therapy.

In a study, intragastric acidification prevented the sustained gastrin release 42. Similarly an intravenous infusion of somatostatin 5 µg / kg / h prevented the sustained meal-stimulated gastrin release (32).

Somatostatin (SMS) has been implicated in the regulation of gastric acid secretion. A paracrine role has been postulated, with both a direct effect on the parietal cell to inhibit acid secretion and an indirect effect on the gastrin cells to inhibit gastrin release being hypothesized (33). Antral D cells have characteristic cytoplasmic projections onto cells that my serve as a pathway for paracrine regulation (34). Further, an inverse relationship between antral gastrin and somatostatin cells has been previously described under varying rates of gastric acid secretion (35).

In a study done in rats, increased antral gastrin concentrations accompanied elevated plasma gastrin levels after omeprazole 400 µmol / kg / day, but not after omeprazole 10 µmol /kg / day or after antrectomy (36). The high omeprazole dose also produced a decrease in antral and fundic SMS concentrations without altering plasma SMS levels (36). Another study in rats treated for four weeks with omeprazole, 400 µmol / kg / day, confirmed that antral tissue concentrations decreased in association with increased plasma gastrin and antral gastrin concentrations (37). Neither study demonstrated any significant differences from control levels of other regulatory peptide tissue concentrations (36,37). These findings suggested a reciprocal relationship between antral gastrin and SMS in rats made achlorhydric by high-dose omeprazole treatment.

In rats made achlorhydric by omeprazole, investigators showed significant early increases in both serum gastrin (within two hours) and gastrin mRNA levels (after 24 hours) (38). They also showed that antral SMS mRNA levels significantly decreased after 24 hours of omeprazole treatment. These omeprazole-induced increased gastrin mRNA and serum levels could be abolished by treatment with a SMS analogue (38). However, SMS 201-995 did not effect the decreased antral SMS mRNA levels observed with achlorhydria (38).

In humans, similar information either after prolonged antisecretory therapy or in pernicious anaemia patients is not available. Pernicious anaemia patients somatostatin-like-immunoreactivity in antral and fundic tissue extracts (39).

Together, these data suggested that antral SMS D cells may regulate gastrin secretion and synthesis in adjacent G cells in response to changes in gastric pH as occurs with achlorhydria.

In conclusion, of this study omeprazole increases serum gastrin level and SMS 201-995 completely abolishes by omeprazole induced hypergastrinemia. Further studies are needed for confirmation of the potential clinical usefulness the inhibitory action of SMS 201-995 on hypergastrinemia resulting from omeprazole treatment in the patients with peptic ulcer disease.

KAYNAKLAR

1. Betton, GR., Dormer, CS?, Wells, T. et al. Gastric ECL-cel hyperplasia and carcinoids in rodest following chronic administration of H2-antagonists SK/F93479 and oxmetidine and omeprazole. Toxicol. Path., 1988; 16; 288-98.
2. Brittan, RT., Jack, D., Reeves, JJ. and Stobles, R. Pharmacological basis for the induction of gastriccarcinoid tumors in the rat by loxtidine, an unsurmountable histamine H2-receptor blocking durg. Br. J. Pharm., 1985; 85; 843-47.
3. Hirth, R. S., Evans, LA., Burchar, RA. and Oleson, FB. Gastric enterochromaffin like cell hyperplasia and neoplasia in the rat : an indirect effect of the histamine H2-receptor antagonist, BL-6341. Toxicol. Path., 1988; 16 : 273-87.
4. Larsson, M., Carlsson, E., Mattsson, H. et al. Plasma gastrin and gastric enterochromaffin-like cell activation and proliferation. Gastroenterology, 1986; 90 : 391-99.
5. Ryberg, B., Mattsson, H., Larsson, H. and Carlsson, E. Correlation between inhibition of gastric acidsecretion, plasma gastrin, and oxyntic mucosal decarboxylase activity in the rat. Scand. J. Gastroenterol., 1989; 24 : 287-92.

6. Inauen, W., Rohner, C., Kolelz, H. K. et al. Enprostil reduces the increase of gastric corpus mucosal mass induced by the hydrogen-potassium stimulate inhibitor BY 831-78 in the rat. Gastroenterology. 1989; 97 : 846-52.

7. Spencer, AJ., Barbolt, TA., Hgury, DC. et al. Gastric morphological changes including carcinoid tumors in animals treated with a potent hypolipidemic agent, ciprofibrate. Toxicol. Pathol., 1989; 17 : 7-15.

8. Larson, GM., Sullivan, HW. and Rayford, P. Omeprazole-induced hypergastrinemia : role of gastric acidity. J. Surg., 1989; 40 : 504-09.

9. Lind, T., Cederberg, C., Forsell, H. et al. Relationship between reduction of gastric acid secretion and plasma gastrin concentration during omeprazole treatment. Scand. J. Gastroenterol., 1988; 23 : 1259-66.

10. Richardson, CT. Effect of H2-receptor antagonists on gastric acid secretion and serum gastrin concentration : a review. Gastroenterology, 1978; 74; 366-70.

11. Walsh, JH., Synik, B., Maxwell, V. et al. Reversibility of plasma gastrin changes induced by omeprazole and ranitidine in man. Am. J. Gastroenterol., 1988; 83 : 1042.

12. Lanzon-Miller, S., Pounder, Re., Hamilton, MR. et al. Twenty-four hour intragastric acidity and plasma gastrin concentration before and during treatment with either ranitidine or omeprazole. Aliment. Pharmacol. Ther 1987; 1 : 239-51.

13. Lanzon-Miller, S., Pounder, RC., Hamilton, MR. et al. Twent-four hour intragastric acidity an plasma gastrin concentration in healthy subjects and patients with duodenal or gastric ulcer, or pernicious anaemia. Aliment. Pharmacol. Ther., 1987; 1 : 225-37.

14. Walsh, JH. Gastrointestinal hormones. In : Physiology of the Gastrointestinal Tract. (Ed. L. R. Johnson). Raven Press, New York, 2nd Edition, 1987; 181-253.

15. Walsh, JH. and Grossman, MI? Gastrin. N. Engl. J Med., 1975; 292 : 1324-34; 1377-84.

16. Walsh, JH. Richardson, CT. and Fordtran, JS. pH dependence of acid secretion and gastrin release in normal and ulcer subject. J. Chn. Invest., 1975; 55 : 462-68.

17. Peters, MN., Feltman, M?, Walsh, JH. and Richardson, CT. Effect of gastric alkalinization on serum gastrin concentrations in humas. Gastroenterology, 1983; 85 : 35-37.

18. Peterson, WL. Walsh, JH. and Richardson, CT. Cimetidine blocks antacid-induced hypergastrineamia. Gastroenterology, 1986; 90 : 48-52.

19. Kovacs, Tog. an Walsh, JH. Gastric secretory testing. In : Principles and Practice of Gastroenterology and Hepatology. (Ed. G. Gitnick), Elsevier, 1888; 270-278.

20. Creuzfeldt J, Arnold R. Metabolism 1978, 27 (suppl 1), 1309-1315.

21. Bloom SR., Mortimer CH., Thorner MO., Messer GM, Hall R., Gomez-Pan A, Roy VM., Russell RC., Kastin AJ., Schally A., Lancet 1974, 2, 1106-1109.

22. Meyers CA., Coy DH., Nuang WY. Biochemistry 1978, 17, 2326-2331.

23. Vale W., Rivier J., Ling N., Brown M. Metabolism 1978, 27 (suppl 1), 1311-1401.

24. Baur W., Briner U., Doepfner W, Haller R., Huguenin R., Marbach P., Petcher P., Pless SMS. Life Sci 1982, 31, 1133-1140.

25. Cadiot, G., Lehy, T. and Bonfils, S. Action of somatostatin analogue (SMS 201-995) on the growth promoting effect resulting from sustained achlorhydria in rat gastric mucosa with special reference to endocrine cell behaviour. Eur. J. Clin. Invest., 1988; 18 : 360-368.

26. Larson, L. I., Hakanson, R., Mattsson H. et al : Omeprazole : Its influence on gastric acid secretion, gastrin and ECL cells. Toxicol. Path., 1988; 16 : 267-72.

27. Simoens, C., Woussen-Calle, M. C. and Degraef, J. Effect of cimetidine, ranitidine and omeprazole on postprandial gastrin and somatostatin release in conscious dogs. Reg. Pep., 1988; 22 : 285-93.

28. Larson, G. M., Sullivan, H. W. and Rayford, P. L. Relationship of omeprazole induced hypergastrinemia to gastric pH Surgery, 1986; 100 : 175-80.

29. Richardson, C. T., Bailey, B. A., Walsh, J. H. et al. The effect of an H-antagonist on food-stimulated gastric acid secretion, serum gastrin and gastric emptying in patients with duodenal ulcers. J. Clin. Invest., 1978; 55 : 536-42.

30. Richardson, C. T. and Feldman, M. Effect of histamine and cimetidine on amino acid meal-stimulated gastrin release at a controlled intragastric pH in healthy human beings. Regul. Pep., 1985; 10 : 333-44.

31. Londong, W., Londong, V., Cederberg, C. and Steffen, H. Dose-response study of omeprazole on meal stimulated gastric acid secretion. Gastroenterology, 1983; 85 : 1373-78.

32. Simoens, C., Woussen-Calles, M. C. and Degraef, J. Effect of acute suppression of acid secretion by omeprazole on postprandial gastrin release in consious dogs. Gastroenterology, 1989; 97 : 837-45.

33. Walsh, J. H. Peptides as regulators of gastric acid secretion. Ann. Rew. Physiol., 1988; 50 : 41-63.

34. Larsson, L. I., Goltermann, N., Demagistis, L. et al. Somatostatin cell process as pathways for paracrine action. Science, 1978; 205 : 1393-95.

35. Arnold, R., Hulst, M. V., Neuhof, C. H. et al. Antral gastrin producing G cells and somatostatin producing D cells in different states of gastric acid secretion. Gut, 1982; 23 : 285-91.

36. Allen J. M., Bishop, A. E., Daly, M. J. et al. Effect of inhibition of acid secretion on the regulatory peptides in the rat stomach. Gastroenterology, 1986; 90 : 970-77.

37. Ryberg, B., Bishop, A. E., Bloom, S. R. et al. Omeprazole and ranitidine, antisecretagogues with different modes of action are equally effective in causing hyperplasia of enterochromaffin-like cells in rat stomach. Reg. Rep., 1989; 25 : 235-46.

38. Brand, J. and Stone, D. Reciprocal, regulation of antral gastrin and somatostatin gene expression by omeprazole-induced achlorhydria. J. Clin. Invest., 1988; 82 : 1059-66.

39. Chayvialle, J. A. P., Descos, F., Bernford, C., et al. Somatostatin in the mucosa of stomach and duodenum in gastroduodenal disease. Gastronenterology, 1978; 75 : 13-19.