Preventive Effect of Pentagastrin on Aspirin-Induced Gastric Lesions

ASPİRİNİN İNDÜKLEDİĞİ GASTRİK LEZYONLARDA PENTAGASTRİNİN KORUYUCU ETKİSİ

Sait KAPICIOĞLU*, Seyfı YILMAZ*, Abdulkadir REİS**,
Abdülhalim BAKİ*, Mehmet SARI*

* Dept. of Internal Medicine, Section of Gastroenterology, Medical School of Karadeniz (Black Sea) Techical University,
** Dept. of Pathology, Medical School of Karadeniz (Black Sea) Techical University, Trabzon, TURKEY

Summary

We investigated whether pentagastrin might prevent gastric mucosal damage induced by intragastric (ig) perfusion of hydrochloric acid (HCI) combined with intravenous (iv) infusion of aspirin (ASA) in rats. Forty rats were divided into two groups. Group A received saline, Group B received pentagastrin 250 ng /kg three times a day for seven days. Each group were divided into two subgroups and received one of the following combinations: Group A I: Saline (iv)+HCl (ig), group A ll: ASA (iv)+HCI (ig), group B 1 :Saline (ig) +HC1 (ig), group B ll: ASA (iv)+HCl (ig). The rats were anesthetized by penthobarbital 50 mg/kg. The cannula was inserted to trachea. Femoral vein was cannulated for venous infusion of saline or ASA. A catheter was inserted into the antrum. The lesion index of stomach was evaluated.

In group A l a gastric lesion score of 0.08±0.04 mm and in group A II a gastric lesion score of 11.86±2.27 mm was observed in gastric mucosa. In the A ll group the mean lesion index was significantly higher than other groups (pO.OOOl, p<0.0005). In group B I gastric lesion score was 1.82±0.25 mm and in group B II 3.32±0.59 mm. The level was less than in group A II (p<0.005). In all groups the pH was between 1.2 and 1.35 and therefore statistically not significant.

In conclusion regular injection of pentagastrin resulted in increase in resistance to aspirin-induced gastric mucosal damage in rats.

Key Words: Pentagastrin, Aspirin, Hydrochloric acid, Gastric lesion, Rat

TKlin J Med Res 2000, 18:105-108

Özet

Bu çalışmada sıçanlarda intragastrik (ig) HC1 perfüzyonu ile birlikte intravenöz (iv) aspirinin (ASA) oluşturduğu gastrik hasara pentagastrinin etkisi araştırıldı. Kırk sıçan iki gruba ayrıldı. A grubuna serum fizyolojik (SF), B grubuna ise 250 ng/kg pentagastrin, günde 3 kez 7 gün süreyle verildi. Her grup 2 alt gruba ayrıldı ve aşağıdaki kombinasyonlardan birini aldı. Grup A l: SF(iv) + HCl(ig), grup A ll: ASA(iv) + HCl(ig), grup BI: SF(ig) + HCl(ig), grup B il: ASA (iv) + HC1 (ig). Sıçanlara 50 mg/kg pentobarbital ile anestezi yapıldı. Trakeaya ve intravenöz ASA ve SF için femoral vene kanül yerleştirildi. Antruma kateter yerleştirildi. Mide lezyon indeksi değerlendirildi. Grup AF de gastrik lezyon skoru 0.08±0.04 mm, grup Ali'de gastrik lezyon skoru 11.86±2.27 mm, Grup Bl'de gastrik lezyon skoru 1.82±0.25 mm idi. A l i grubunda lezyon skoru diğer gruplardan (A l ve BI) anlamlı derecede yüksekti. (pO.OOOl, p<0.000.5) Grup BU'de ise gastrik lezyon skoru 3.32±0.59 mm idi. Bu gruptaki lezyon skoru Grup AH' den düşüktü. (p<0.005) Tüm gruplarda pH 1.2-1.35 arasında idi ve gruplar arasındaki fark istatistiksel olarak anlamsızdı.

Sonuç olarak düzenli pentagastrin injeksiyonunun sıçanlarda aspirin ile oluşturulan gastrik mukozal hasara karşı koruyucu olduğu gösterilmiştir.

Anahtar Kelimeler: Pentagastrin, Aspirin, Hidroklorik asit, Gastrik lezyon, Sıçan

T Klin Araştırma 2000, 18:105-108

Received: Oct. 23, 1999

Correspondence: Sait KAPICIOGLU
Dept. of Internal Medicine, Section of Gastroenterology, Medical School of Karadeniz (Black Sea) Techical University
61080, Trabzon, TURKEY

Pentagastrin has been shown to have a cytoprotective effect on the gastric mucosa by the mechanisms that are not yet understood (1-4). Subcutaneous injections that pentagastrin protected against stress induced gastric ulcers and this effect

was releated to pentagastrin trophic action on the mucosa (5-7). Johnson and Guthrie compared the trophic effects of pentagastrin and epidermal growth factor on gastrointestinal mucosa and found that both peptides stimulated synthesis of DNA, RNA, and protein in oxyntic gland mucosa in rats (8). Pentagastrin, appears to stimulate somatostatin (SMS) directly by stimulation of D cells, and indirectly by inducing gastric acid secretion (9). Somatostatin (SMS) can potentiate the synthesis and release of endogenous prostaglandin E_2 (PGE_2) from the isolated rat stomach. Prostaglandins are well known as cytoprotective agents and a potent inhibitor of gastric acid secretion (10-13). It is conceivable that pentagastrin may stimulate SMS synthesis and release which may result in the synthesis of endogenous PGE_2.

In the present study we attempted to show whether pentagastrin can prevent aspirin induced gastric lesions in rats.

Materials and Methods

Forty male Sprague-Dawley rats, weighing approximately 200g were divided into two groups. Members of each group were given one of the following subcutaneous injections.

Group A: Saline (n:20)

Group B: Pentagastrin 250 ng/kg (n:20) (Peptavlon, Ayerst laboratories, New York NY) (5).

Injections were made three times a day for seven days, while the rats were housed individually in wire cages and fed with a regular diet. Before the operation, rats were fasted for 24 hours with free access to water. Each group divided into two subgroups (n:10) and received one of the following combinations:

Group A I: (n:10) Saline iv + HCI ig

Group A II : (n:10) ASA iv + HCI ig

Group B I : (n:10) Saline ig + HCI iv

Group B II : (n:10)ASA iv + HCI ig

The rats were anesthetized by intraperitoneal administration of sodium penthobarbital (Nembutal) 50 mg/kg. A midline neck incision was cannulated to insure ventilation. Femoral vein was also cannulated for venous infusion of saline or ASA. Next, a midline abdominal incision was made for a duodenostomy, a catheter was inserted into the antrum from the duodenum through the pylorus for gastric juice collection. An orogastric (o.g) tube also placed for the gastric perfusion of HCI (0.15 N HCI). The pylorus was ligated with free ties around the tube.

A solution of ASA was freshly prepared at the beginning of each test by dissolving 3 g of $NaHCO_3$ and 3 g of ASA in 100 ml of distilled water. The final concentration of solution was ASA 30 mg/ml. The solution further diluted with saline to give a desired dose for intravenous (iv) administration. ASA given in a standart iv bolus dosage of 60mg/kg followed by a constant iv infusion of 40 mg/kg/h by Harvard infusion pump. The same iv dose of ASA was used by Kouffman and Grossman (14) to produce gastric ulcerations in rats. Simultaneous gastric perfusion with 0.15 N HCI was carried out via the o.g. tube at a rate of 4 ml/h by Gilson Minipuls. I.v. ASA infusion and intragastric (ig) HCI perfusion was carried out for three hours (15). At the termination of the experiment, the animals were killed by air embolism, the stomach opened along the greater curvature. The stomachs was observed for the presence of gastric mucosal lesions by blinded observers. The ulcerated area was planimetrically measured and the lesion index evaluated according to Brodie (16). With the aid of dissecting microscope (xlO), we calculated the average length of each lesion in mm and used as the ulcer index (17,18).

Student's t-test was used for the statistical analysis of the data.

Results

The results are summarized in figure 1. The gastric lesion score in the gastric mucosa was 0.08 ± 0.04 mm in group A I and 11.86 ± 2.27 mm in group A II. In this group the mean lesion index was significantly higher than in other groups ($p<0.0001$, $p<0.0005$). The gastric lesion score was 1.82 ± 0.25 mm in group B I and 3.32 ± 0.59 mm in group B II. The level was less than in group A II ($p<0.005$). In all groups the pH value was between 1.2 and 1.35 (statistically not significant).

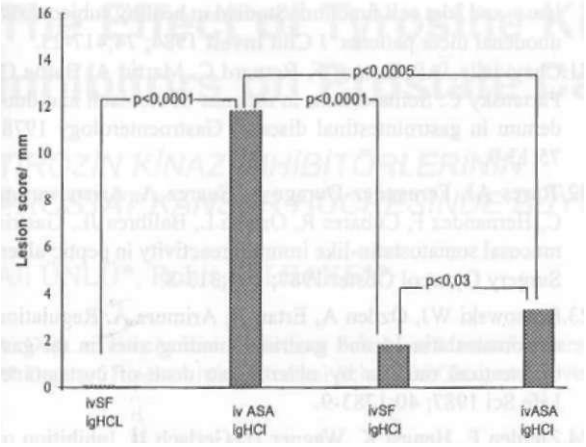

Figure 1. Effects of chronic administration of saline or pentagastrin on aspirin-induced gastric lesion (X ± SEM).

Discussion

This study demonstrated that chronic treatment with pentagastrin reduces aspirin-induced gastric lesions in rats, although pentagastrin has opposite effects on gastric acid secretion. Pentagastrin exert cytoprotective activity on gastric mucosa by mechanisms that are not entirely understood.

In a study, it was reported that injections of pentagastrin protected rats, which had been depleted of gastrin, against stress ulcer and provided evidence that, the cytoprotective effect of pentagastrin was related to its trophic action (7). On the other hand, the trophic effects of pentagastrin on gastrointestinal mucosa was shown and found that a peptide stimulates synthesis of DNA, RNA, and protein in oxyntic gland mucosa in rats (8). The anti-ulcer effects of pentagastrin may, therefore be releated in part to increased synthesis of DNA (16). Therefore, these anti-ulcer effects provided by pentagastrin may be in part attributed to its trophic action on gastric mucosa.

A study demonstrated that chronic administration of pentagastrin resulted in significantly higher antral somatostatin like immunoreactivity (SLI) (5). During exposure to stress, antral SLI was markedly decreased in rats (5).

Somatostatin stimulates gastric mucus production (19) and alters the target cells that control acid secretion and gastrin release (20). Somatostatin may effect the pathogenesis of peptic ulcer disease by providing both cytoprotection and an agressive acid-pepsin factor (21-23). Studies demonstrated that exogenous administration of somatostatin (SMS) prevented stress ulcer-induced gastric lesions in rats (24,25). Recently we have demonstrated that SMS inhibits gastric acid secretion and iv ASA/ig HCl-induced ulcer induction and increased SLI concentration in gastric juice (26). Somatostatin can potentiate the synthesis and release of endogenous PGE_2 (26). Prosta-glandins are well known as cytoprotective agents and potent inhibitors of gastric acid secretion (10,11,27).

It is therefore conceivable that, pentagastrin may stimulate SMS synthesis and release which may in turn, stimulate synthesis of endogenous PGE_2.

In conclusion, chronic injection of pentagastrin provides an increase in resistance to aspirin-induced gastric mucosal damage in rats.

REFERENCES

1. Tanaka S, Akiba Y, Kaunitz JD. Pentagastrin gastroprotection against acid is related to 112 receptor activation but not acid secretion. Gut 1998; 43;334-41.

2. Komuro Y, Ishihara K, Ohara S, Saigenji K, Hotta K. Effects of tetragastrin on mucus glycoprotein in rat gastric mucosal protection. Gastroenterol Jpn 1992; 27;597-603.

3. Konturek SJ, Brzozowski T, Bielanski W, Schally AV. Role of endogenous gastrin in gastroprotection. Eur J Pharmacol 1995; 278;203-12.

4. Dodig M, Rotkvic I, Grabarevic Z, Sikiric P, Drahotusky T, Erceg D, Dacic S, Seiwerth S. Pentagastrin cytoprotection in ethanol-induced gastric mucosal lesions in rats. Zentralbl Veterinarmcd 1993; 40; 509-15.

5. Sakamoto T, Swierczek JS, Ogden WD, Thompson JC. Cytoprotective effect of pentagastrin and epidermal growth factor on stress ulcer formation. Possible role of somatostatin. Ann Surg 1985; 201;290-5.

6. Li D, Dai Y, Chen Q, Xido Q, Zhu Q. Protective effect of pentagastrin against stress-induced gastric lesions in rats. Chin Med J 1986; 99;457-60.

7. Takeuchi K, Johnson LR. Pentagastrin protects against stress ulceration in rats. Gastroenterology 1979; 76;327-34.

8. Johnson LR, Guthrie PD. Stimulation of rat oxyntic gland mucosal growth by epidermal growth factor. Am J Physiol 1980; 238;45-9.

9. Ertan A, Arimura A. Somatostatin ad the stomach. Dis Dis 1987; 5;13-20.

10. Ligumsky M, Goto Y, Debas II, Yamada T. Prostaglandins mediate inhibition of gastric acid secretion by somatostatin in the rat. Science 1983; 219;301-3.

11. Robert A, Negamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats: Prevention of gastric necrosis produced by alcohol, HCI, NaOH, hypertonic NaCI and thermal injury. Gastroenterology 1979; 77;433-43.

12. Robert A. Cytoprotection by prostaglandins. Gastroenterology 1979; 77;761-7.

13. Robert AR, Schultz JR, Nezamis JE, Lancaster C. Gastric antisecretory and antiulcer properties of PGE2, 15-methyl PGE2 and 16,16-dimethyl PGE2: Intravenous, oral and intrajejunal administration. Gastroenterology 1976; 70;359-65.

M. Kauffman G, Grossman M. Prostaglandin and cimetidine inhibit the formation of ulcers produced by parenteral salicylate. Gastroenterology 1978; 75; 1099-102.

15. Konturek SJ, Brozozowski T, Piatucki L, Tradecki T. Prevention of ethanol and aspirin induced gastric mucosal lesions by paracetamol and salicylate in rats: Role of endogenous prostaglandins. Gut 1982; 23;536-40.

16. Brodie DA, Hansom H M. A sudy of the factors involved in the production of gastric ulcers by the restraint tehnique. Gastroenterology 1980; 38;353-6

17. Konturek SJ, Radecki T, Brzozowski T, Piastucki I, Dembiski A, Dembiska KIEC. Gastric cytoprotection by epidermal growth factor role of endogenous prostglandins and DNA synthesis. Gastroenterology 1981; 81;438-43.

18. Hayase M, Takeuchi K. Gastric acid secretion and lesion formation in rats under water-immersion stress. Dig Dis Sci 1986;31;166-71.

19. Johansson C, Aly A. Stimulation of gastric mucus output by somatostatin in man. Eur J Clin Invest 1982; 12;37-9.

20. Colturi TJ, Unger RH, Feldman M. Role of circulating somatostatin in regulation of gastric acid secretion, gastrin release, and islet cell function: Studied in healthy subjects and duodenal ulcer patients. J Clin Invest 1984; 74;417-23.

21. Chayvialle JAP, Descos F, Bernard C, Martin A, Barbe C, Partensky C. Somatostatin in mucosa of stomach and duodenum in gastrointestinal disease. Gastroenterology 1978; 75;13-9.

22. Torres AJ, Femandez-Durago L, Suarez A, Ariznavarreta C, Hernandez F, Cubares R, Ortega L, Balibrea JL. Gastric mucosal somatostatin-like immunoreactivity in peptic ulcer. Surgery Gynecol Obstet 1987; 164;313-8.

23. Rossowski WJ, Ozden A, Ertan A, Arimura A. Regulation of somatostatin-14 and gastrin-1 binding sites in rat gastrointestinal mucosa by ulcerogenic dose of cysteamine. Life Sci 1987; 40; 1783-9.

24. Zierden E, Hengst K, Wagner H, Gerlach U. Inhibition of stress ulcer formation with somatostatin in rats. Res Exp Med 1976; 168;199-201.

25. Kapicioglu S, Ovah E, Bans YS. Inhibition of stress ulcer formation with Somatostatin Anologue (SMS 201-995) in rats. Turkish J Gastroenterology 1992; 3;135-8.

26. Kapicioglu S, Arimura A, Yeginsu O, Mancada A, Ertan A. Effect of Tyrl-somatostatin on aspirin and hydrochloric acid-induced gastric ulcer in rats Gastroenterology 1988; 94;A216.

27. Robert AR, Schultz JR, Nezamis JE, Lancaster C. Gastric antisecretory and anti-ulcer properties of PGE2, 15-methyl PGE2 and 16.16-dimethyl PGE2: intravenous, oral and intrajejunal administration. Gastroenterology 1976; 70;359-63.