Action of Verapamil On Aspirin-Induced Gastric Lesions in Human

Dr. S. KAPICIOĞLU, Dr. Ş. TARLAN, Dr. E. OVALI, Dr. A. H. BAKİ,
Dr. M. KARAKOÇ, Dr. N. KAYA

Özet: ASPIRIN İLE OLUŞTURULAN MİDE LEZYONLARININ VERAPAMİLİLE ÖNLENMESİ

Kalsiyumun hücre içine akışı parietal hücrelerden asit sekresyon aktivasyonunda önemli bir noktadır. Peptik ülser patogenezinde hiperasidite odak noktasını oluşturmaktadır. Kalsiyum kanal blokerlerinin stimüle edilmiş asit sekresyonunu inhibe ettiği kliniğimizdeki çalışmalarla da gösterilmiştir. Ancak verapamil'in kimyasal ajanlarla oluşturulan ülserlere etkisi hakkındaki bilgilerimiz açık değildir. Bu nedenle randomize, çift kör, plasebo kontrollü çalışmamızda bir kalsiyum kanal blokeri olan verapamil'in aspirin ile oluşturulan gastrik lezyonların önlenmesindeki etkileri ranitidin ile karşılaştırmalı olarak incelenmiştir. Otuz sağlıklı erkek gönüllü üç gruba ayrıldı. Gönüllüler gece yarısı verapamil 240 mg(n:10), ranitidin 300 mg(n:10) veya plasebo (n:10) aldılar. İlaçlardan 8 saat sonra aspirin 1g verilerek bundan 4 saat sonra da endoskopi uygulandı. Gastrik mukozadaki lezyonlar skorlandı. Plasebo grubunda lezyon skoru 2.7±0.6 iken verapamil alan vakalarda lezyon skoru 2.1±0.5'e düştü. Lezyon sayısındaki azalma istatistiki olarak anlamsızdı. Ranitidine ise aspirin'in yaptığı lezyonları tamamen önledi. Lezyon skoru 0.02±0.01 idi (p 0.000001). Bulgular, aspirin ile oluşturulan gastrik lezyonları verapamil'in anlamlı bir şekilde önliyemediğini, ancak ranitidin'in etkin bir şekilde koruduğunu göstermektedir. Verapamil'in antiülserojenik etkilerine dair bulgular olmasına rağmen etkili bulunmaması, doza bağlı yeni çalışmalara ihtiyaç olduğunu düşündürmektedir.

Anahtar Kelimeler: Verapamil, Ranitidine, Aspirin, gastric damage, İnsan.

Summary: *This randomized, double-blind, placebo-controlled study compared the preventive effect of verapamil and ranitidine on aspirin-induced gastric mucosal damage. Thirty healthy subjects have devided into three groups. The subjects have received verapamil 240 mg(n:10) (Knoll. Co. Turkey), ranitidine 300 mg(n:20) (Glaxo, Co) at midnight, aspirin 1 gr (Bayer) six hours later of verapamil, ranitidine or placebo receiving. Placebo(n:10) have correspoinded to verapamil, or ranitidine. The gastric mucosa was graded using a seven-point endoscopic scale by endoscopists four hours later of aspirin administration. The gastric mucosa of placebo-treated subjects had damage 2.7±0.6 (mean±SEM) with endoscopic score. Verapamil reduced gastric mucosal injury (20.0 %) with a mean endoscopic score 2.1±0.5, this effect was not statistically significant. Ranitidine totally abolished (99.9 %) an aspirin-induced gastric lesions with and endoscopic score of (0.02±0.01) as compared to placebo p(0.000001) and to verapamil p 0.00001. In conclusion verapamil 240 mg showed no significant difference from placebo in preventing mucosal damage, was induced by aspirin induced-ulcer formation. Ranitidine significantly reduced gastric lesion. There are many possible reasons why such a results are suprising in view of further evaluate anti-ulcer effect of verapamil are recommented.*

Key Word: Verapamil, Ranitidine, Aspirin, gastric damage, human.

Department of Medicine, Gastroenterology Section, School of Medicine, Ondokuz Mayıs University and Section of Surgery, Military Hospital, Samsun, TURKEY

Calcium (Ca) plays an important role in the regulation of gastric acid secretion (1-6); however the exact mechanism by which Ca influences parietal cell is unknown. It remains controversial whether any of the three classes of Ca channel antagonists can influence gastric acid secretion. Previous work by our clinics and others showed that parenteral verapamil inhibited pentagastrin-stimulated gastric acid secretion in human and also reduced gastric acid secretion and stress-and ethanol-induced gastric ulcer in rats (7-13). In contrast, others demonsrated that verapamil did not alter basal or near-maximal pentagastrin-stimulated gastric acid secretion in humans (13-15). It is demonsrated that inhibition of gastric acid secretion in parietal cell by verapamil may not involve Ca channel antagonism (16). Rather, these drugs inhibit directly the H^+, K^+-ATPase pump under acidic conditions by interfering with the high affinity K+ -site of the H^+,K^+, -AtPase system which is accessible from the luminal side of the stomach (16).

The aim of the present study were to investigate the possible protective action of verapamil and ranitidine against gastric mucosal injury induced by aspirin and to compare this effect to the protection provided with each other.

MATERIAL and METHODS

Thirty healthy adult male volunteers have studied in randomized, double-blind, placebo-controlled. Their age range were (20±0.1) years. Subjects had no history of smoking, or of taking nonsteroidal anti-inflammatory analgesics, or antisecretory use. They ingested no medication for at least 15 days prior 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, including platelet count, protrombin time and activated partial thromboplastin time. Gastrointestinal blood loss have measured in each subject.

Table I: Endoscopic grading of gastric mucosal changes*.

Grade	
0	Normal mucosa
1	Localized or diffuse hyperemia
2	
3	1
4	2-5
5	5-10 Submucosal hemorrhagic lesions
	10
6	or large area of confluent hemorrhagic lesions Erosions with bleeding

* Agrawal NM, et al [17].

The subjects have received verapamil 240 mg (n:10) (Knoll A.G.), ranitidine 300 mg(n:10) (Glaxo, Co) at midnight, and aspirin 1 gr (Bayer) received, six hours later of verapamil ranitidine or placebo receiving. Placebo (n=10) have correspointed to verapamil, ranitidine or aspirin. The order of treatments have randomised according to a latin square desing and the study conducted in double blind mamer. Through the utilization, of this system, neither the endoscopists nor any personnel in the endoscopy room, nor subjects have awared of the treatments being given to the subjects.

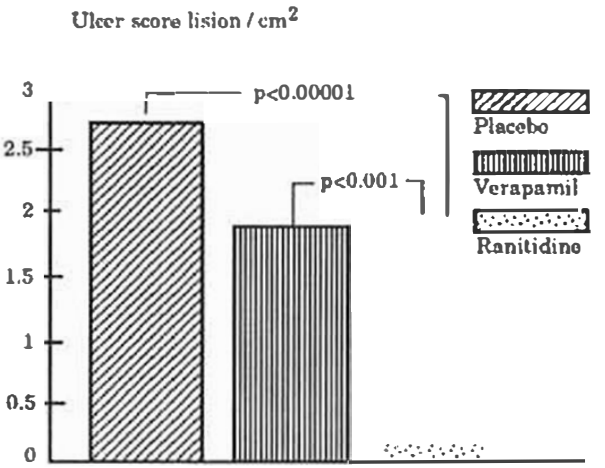
Subjects have admidted to the study unit after a 12-hour overnight fast. Each participant received either verapamil ranitidine, aspirin or placebo with 30-90 ml of water four hours later of aspirin administration esophagogastroduodenoscopy have performed, using an Olympus GIF Q10 gastroscop (Olympus Co. of JAPAN) and hypopharyngeal anesthetic have performed by Lidocain. Intravenous diazem have given as necessary for sedation. Gastric mucosa have observed for gastric damage. Quantitative classification of endoscopic damages in the gastric mucosa have based on criteria shown in table I (17).

The gastric mucosa have observed continuo-

Table II: Gastric endoscopic scores at 4 hours after aspirin administration.

	Mean endoscopic score±SEM		
	Placebo n:10	Verapamil* n:10	Ranitidine** n:10
		240mg	300mg
Aspirin 4 hours later	2.7±0.6	2.1±0.5	0.02±0.01

* p<0.05 compare to ranitidine p<0.00001
** p<0.01 compare to placebo p<0.000001



Graphic 1: Gastric endoscopic scores at 4 hours after aspirin administration.

usly and evaluated independently by endoscopist blinded as to the treatment.

The primary statistical analysis have performed separately for the endoscopic scores. The scores have averaged for each subject and a kruskal-Wallis test16 have used to compare the four teratment groups. In-depth, pairwise comparisons between each two treatments have also carried out at the 5% significance level, following Fisher's LSD principle (19).

RESULTS

The gastric mucosa of placebo-treated subjecsts had damage 2.7±0.6 with endoscopic score verapamil prevented gastric mucosal injury (20.0 %) with a mean endoscopic score of 2.1±0.5 (mean±standard error mean-M±SEM) when compared to placebo, but this difference was not significantly. Ranitidine totally abolished (99.9 %) on aspirin induced gastric lesions with an endoscopic score of (0.02±0.01) as compared to placebo (p 0.000001) and to verapamil (p 0.00001) (table II, Graphic 1).

DISCUSSION

This study showed a statistically significant a statistically significant advantage of ranitidine of verapamil in reducing gastric mucosal lesions. A clinical trial 300mg ranitidine per day, would therefore be justified in patients at risk of gastric damage from aspirin.

Otherwise, verapamil 240 mg showed no significant difference from the placebo in preventing mucosal damage from 1 g aspirin therapy. There are many possible reasons why such a result may have occured, but the results are suprising in view of the strong positive experimental evidence of verapamil. Future studies to further evaluate for preventive effect of verapamil are recommended.

However, in this study, verapamil decreased 20.0 percent gastric damage induced by aspirin. Verapamil inhibit histamin-stimulated production, gastric acid secretion, but not basal levels. These mechanisms therefore can account for its therapeutic properties.

Verapamil are reversible, relatively selective inhibitors of H^+, K^+ -ATPase (15). Inhibition of acid production in parietal cell is due to an accumulation of these drugs into the acidic secretory channel, thus impairing H^+, K^+ - ATP ase. It appears that the reactive species of this weak base is the protonated charged form. In the intact cell, in protonated form to a luminal rather than a cytosolic site could prevent acid secretion (15). The inhibitory action of verapamil on histamin-stimulated parietal cell was reserved after buffering the acid spaces by imidazol (15). Two possibilities were considered to explain such findings. First, ve-

rapamil is a weak base, its accumulation could be reduced as the pH of the canalicular space was elevated by imidazole, second, verapamil's activity is reduced in its non protonated or neutral form.

Verapamil inhibited H^+,K^+ -ATPase and pNPase activities in competition with K^+ (16). The inhibition of these enzymes were pH sensitive (15).

Inhibition of parietal cell H^+, K^+ -ATPase represents a potential beneficial property in development of future antiulcer drugs, as indicated by the substituted benzimidazoles (20,21) and by a new group of sulfoxide agents, both of which also proven to be potent inhibitors of gastric H^+,K^+ -ATPase (22).

KAYNAKLAR

1. Berglindh T, Sachs G, and Takeguchi N. Ca dependent secretagogue stimulation in isolated rabbit gastric glands. am J Physiol 1980;239:G90-G94.
2. Takeguchi N, Nishimura Y, and Horikoshi I. Ca removal effects on bullfrog gastric mucosa in presence of drug. Jpn J Physiol 1980;30:877-886.
3. Muallem S, and Sachs G. Ca motabolism during cholinergic stimulation of acid secretion. Am J Physiol 1985;G216-G228.
4. Chew CS. Chelocystokinin, carbachol, gastrin, histamine, and forskolin increase (Ca2+)i in gastric glands. Am J Physiol 1986;C130-C140.
5. Mardh S, Song YH, and Wallamark B. Effects of some antisecretory drugs on acid production, intracellular free Ca, and cyclic AMP production in isolated pig parietal cells. Scand J Gastroenterol 1988; 23:977-982.
7. Kaya N, Ovalı E, Kapıcıoğlu S. Effect of Verapamil on Histamine-stimulated gastric acid secretion in human. Turkish Gastroenterohepatology (In press).
8. Sonnenberg A, Kurosinski I, Eckhardt V, and Scholten T. The effect of calcium antagonist verapamil on gastric acid secretion in humans. Hepatogastroenterology 1984;31:80-84.
9. Kirkegaard P, Christiansen J, Petersen B, and Skovolsen P. Calcium and stimulus-secretion coupling in gastric fundic mucosa. Scand J Gastroenterol 1982;17:533-538.
10. Ogle CW, Cho CH, Tong MC, and Koo WL. The influence of verapamil on the gastric effects of stress in rats. Eur J Pharmacol 1985;112: 399-404.
11. Glavin GB. Verapamil and nifedipine effects on gastric acid secretion and ulcer formation in rats. J Pharm Pharmacol 1988;40: 514-515.
12. Glavin GB. Calcium channel modulators: Effects on gastric function. Eur J Pharmacol 1989;160:323-330.
13. Levino RA, Petokas S, Starr A, and Eich RE. Effect of verapamil on basal and pentagastrin-stimulated gastric acid secretion. Clin Pharmacol Ther 1983;34:399-403.
14. Aadland E, and Berstad A. Effect of verapamil on gostric secretion in man. Scand J Gastroenterol 1983;18:969-971.
15. Nandi J, King RL, Kaplan DS, Levin RA. Mechanisms of gastric proton pump inhibition by calcium channel antagonists. J Pharm and Exp Ther 1990;252:1102-1108.
16. Im WB, Blakeman DP, Mandein J, and Sachs G. Inhibition of (H+,K+)-ATPase and H+ accumulation in hog gastric membranes by trifluoperozine, verapamil and 8-(N,N-diethylamino) octyl-3,4,5-trimethoxybenzoate. Biochem Biophys Acta 1984;770:65-72.
17. Agrawal NM, Godiwala T, Arimura A, Dajani E. Cytoprotection by a synthetic prostaglandin against ethanol-induced gastric mucosal damage. Gastrointestinal Endoscopy 1986;32:67-70.
18. Covoner WJ. Practical nonparametric statistics. 2nd ed. New York. John Wiley and Sons, 1980.
19. Milliken GA, Johnson DJ. Analysis of messy data, Vol 1: designed experiments. Belmont California: Lifetime Learning Publications, 1984.
20. Fellenius E, Berglindh T, Sachs G, Ollee L, Elander B, Sjpstrand SE, and Wallamark B. Suhstituted benzimidazoles inhibit gastric acid secretion by blocking (H++K+)-ATPase. Nature (Lond). 1981;290:159-161.
21. Wallamark B, Briving C, Fryklund J, Munson K, Jackson R, Mandlein J, Rabon E, and Sachs G. Inhibitor of gastric H+, K+-ATPase and acid secretion hy SCH 28080, a suhstituted pyndyl (1,2a) imidazole. J Biol Chem 1987;2077-2084.
22. Nelson KS, Krasso A, Mullor RKM, and Fischli AE. Ro 18-5364, a potent new inhibitor of gastric (H+,K+)-ATPase. Eur J Biochem 1987;166:453-459.