Preventive Effect Of Omeprazole and Ranitidine on Aspirin-Induced Gastric Mucosal Damage

(A double-blind endoscopic study in human subjects)

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Özet: ASPIRIN'İN OLUŞTURDUĞU GASTRİK LEZYONLARIN ÖNLENMESİNDE OMEPRAZOLE VE RANITIDIN'IN ETKISI

Omeprazole bir asit sekresyon inhibitörü olarak peptik ülser iyileşmesindeki etkisi yanında antiinflamatuvar ilaçların oluşturduğu lezyonların önlenmesindeki rolü açık olarak bilinmektedir. Randomize, çift kör, plasebo kontrollü bu çalışmamızda omeprazole'ün aspirin ile oluşturulan gastrik lezyonların önlenmesindeki etkisi ranitidin ile karşılaştırmalı olarak incelenmiştir. Yaş ortalaması 20±1 olan 30 sağlıklı gönüllüden 1. gruba n:10 plasebo ve 2. gruba n:10 omeprazole (20 mg), 3. gruba n:20 ranitidin (300 mg) ve tüm gruba 8 saat sonra aspirin(1 gr) verilerek 4. saatte endoskopi uygulandı. Gastrik lezyonlar skorlandı. Plasebo grubunda lezyon skoru 2.7±0.6 iken omeprazole grubunda 1.25±0.04 idi (p<0.05). Ranitidin grubunda ise mukozal zarar %100 önlendi ve lezyon skoru 0.02 idi (p<0.00001). Bulgular omeprazole ve ranitidin'in aspirin'le oluşturulan gastrik lezyonları etkin bir şekilde önlediğini göstermekteydi. Ancak bu koruyuculukta ranitidin omeprazole'den daha patent bir etkide tesbit edilmiştir.

Anahtar Kelimeler: Omeprazol, Ranitidin, Aspirin, Gastrik lezyon, İnsan

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Summary: This randomized, double-blind, placebo-controlled study compared the preventive effect of omeprazole and ranitidine on aspirin-induced gastric mucosal damage. Fourty healthy subjects have divided into four groups. The subjects have received omeprazole 20mg(n= 10) (İltaş Co, Turkey), ranitidine 300 mg (n= 20) (Glaxo, Ca) at midnight, aspirin 1 gr (Bayer) six hours later of omeprazole, ranitidine or placebo receiving. Placebo (n= 10) have correspointed to omeprazole, ranitidine or aspirin. 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. Omeprazole significantly prevented gastric mucosal injury(55.6 %) with a mean endoscopic score of 1.25±0.6 when compared placebo. Ranitidine totally abolished (100 %) on aspirin-induced gastric lesions with an endoscopic score of (0.02± 0.01) as compared to placebo (p<0.000001) and to omeprazole (p<0.00001). This study demonstrates that omeprazole and ranitidine have a statistically significant preventive effect on aspirin-induced gastric lesions, when compared to placebo and ranitidine more potent than omeprazole. This preventive effect of omeprazole and ranitidine may prove to be clinically very important and warrants further investigation.

Key Words: Omeprazole, Ranitidine, Aspirin, gastric damage, human.

Aspirin(ASA) and non-steroidal antiinflammatory drugs are strongly associated with peptic ulcer complications in the elderly[1-4]. Assuming that the association may be causative, a number of approches have tried to reduce the extent of damage caused by these agents[5]. Although old people appear to be at greatest risk, it is difficult to evaluate possible therapeutic manoeuvres in this population. Some investigators have therefore investigated healthy adult volunteers whose acute responses appear to reflect those of older patients[6]. Our previous study show that ASA induced gastric lesions were decreased by H_2 receptor blockers but were not totally abolished[7].

It has shown that cytoprotection in that mean gastric lesion scores on aspirin plus HCl induced were significantly reduced by doses of H_2 receptor blockers with and without antisecretory activity[9,10,11].

Omeprazole, a substituted benzimidazole, is a new long acting, patent, and highly specific inhibitor of gastric acid secretion. Unlike H_2 receptor antagonists it appears to act by specific non-competitive interaction with the gastric "proton-pump", blocking (H^++K^+) ATPase located in the secretory membrane of the parietal cell[12]. Its antisecretory action has been confirmed[13-15] and the compound has been shown to prevent ulcer formation by a variety of methods, including pylorus ligation and exposure to aspirin solution.

It is well know that aspirin-produces gastric mucosal lesions in human beings[17] and in mammals[10-12]. The severity of these lesions may be exacerbated by intragastric (ig) perfusion of hydrochloric acid (HCl)[18-22].

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

MATERIAL and METHODS

Fourty 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.

The subjects have received omeprazole 20 mg (n=10) (İltaş Co., Turkey), ranitidine 300 mg (n= 20) (Glaxo, Co) at midnight, and aspirin 1 gr (Bayer) received, six hours later of omeprazole, ranitidine or placebo receiving. Placebo (n= 10) have correspointed to omeprazole, ranitidine or aspirin. The order of treatments have randomised according to a latin square design and the study conducted in double blind manner. Through the utilization, of this system, neither the endoscopists nor any personnel in the endoscopy room, nor subjects have awared of the treatments beign given to the subjects.

Subjects have admitted to the study unit after a 12-hour overnight fast. Each participant received either omeprazole, 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

Table I: Endoscopic grading of gastric mucosal changes*.

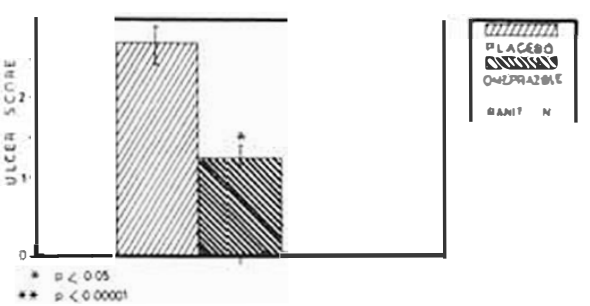
0	Normal mucosa	
1	Localized or diffuse hyperemia	
2	1	Submucosal hemorrhagic lesions
3	2-5	
4	6-10	
5	>10	
6	or large area of confluent hemorrhagic lesions Erosions with bleeding	

* Agrawal NM, et al 23.

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

	Mean endoscopic score ±SEM		
	Placebo n=10	Omeprazole* n=10 20 mg	Ranitidine** n=20 300 mg
Aspirin 4 hours later	2.7±0.6	1.25 ± 0.6	0.02 ± 0.01

*p<0.05, ** p<0.0000001



Graphic 1: Ulcer Score in the gastric mucosa for the three treatment groups (mean ± SEM)

mucosa have observed for gastric damage. Quantitative classification of endoscopic damages in the gastric mucosa have based on criteria shown in table I [23].

The gastric mucosa have observed continuously 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 test[24] have used to compare the four treatment groups. In-depth, pairwise comparisons between each two treatments have also carried out at the 5% significance level, following Fisher's LSD principle[25].

RESULTS

The gastric mucosa of placebo-treated subjects had damage 2.7±0.6 with endoscopic score omeprazole significantly prevented gastric mucosal injury (55.6%) with a mean endoscopic score of 1.25±0.6 (mean±standard error mean-M±SEM) when compared to placebo ($p<0.05$). Ranitidine totaly abolished (100%) on aspirin induced gastric lesions with an endoscopic score of (0.02±0.01) as compared to placebo ($p<0.000001$) and to omeprazole ($p<0.00001$) (Table II, Graphic 1).

DISCUSSION

It is well known that aspirin produces gastric mucosal lesions in human beings[17] in mammalians[18-22]. Widespread use of aspirin and other non-steroidal antiinflammatory drugs has been implicated in peptic ulcer perforation rates[4]. Emergency admission because of bleeding from gastric and duodenal ulcers in the elderly is associated with aspirin and other non-steroidal anti-inflammatory drug use in the hospital population[26]. Aspirin ingestion is associated with a relative risk of three, even for short periods of exposure[1,26]. Moreover, aspirin can provoke gastric mucosal bleeding a doses of up to 75 mg taken daily for five days or less[26]. It is evident that aspirin is probably responsible for a spectrum of damage, ranging from acute gastric erosions to peptic ulcer complications.

In our present study shown that ranitidine and omeprazole prevented on aspirin-induced gastric lesions. Our findings accord with recently reported which showed prevention by

omeprazole of gastric injury after a single aspirin dose[27].

It is well known that severity of aspirin-induced gastric lesions may be exacerbated by intragastric perfusion of hydrochloric acid (HCl)[18-22]. The dissociation constant (pKa) of aspirin is 3.5. The levels of intragastric pH have achieved by omeprazole and ranitidine[27,28], aspirin ionisation is virtually complete. In this form passive absorption of aspirin into the gastric mucosa does not occur[29]. In contrast, at normal intragastric pH aspirin is almost entirely unionised and able to diffuse passively into cells of the gastric epithelium where a neutral pH results in reionisation and intracellular trapping of salicylate in high concentrations. The consequent topical toxicity of salicylates is well recognised and results in impaired barrier function, reduced mucus and bicarbonat secretion, and capillary injury[20,30]. The underlying metabolic changes are not firmly established, but in the presence of acid aspirin may achieve intracellular with carbohydrate metabolism[31]. As most other non-steroidal antiinflammatory drugs are weak acids, similar considerations are likely to apply although direct evidence is lacking.

Apart from these specific benefits, acid inhibition may result in other non-specific advantages. Gastric acid enhances mucosal injury caused by a variety of stimuli[32] and damages the basal lamina resulting in impaired epithelial restitution[33]. In addition, the activity of pepsin is pH dependent and is inhibited at high pH. Whatever the mechanism, the observations presented here strongly support the hypothesis that gastric acid is crucial in the genesis of aspirin-(and possibly other non-steroidal anti-inflammatory drug-) related gastroduodenal injury.

It is possible, however, that oral omeprazole protects the gastric mucosa by additional acid independent mechanisms. In animals, omeprazole given by the oral route is much more effective than when given parenterally in preventing aspirin induced gastric damage despite complete inhibition of gastric acid[34,35]. In addition, oral omeprazole protects against ethanol induced gastric damage if given between 15 to 60 minutes before ethanol, there being no effect evident 3.5 h after the dose. This protective effect of omeprazole is not mediated through gastric mucosal prostaglandins[36], changes in gastric mucosal blood flow[37], or alterations in gastric mucosal bicarbonate secretion[38]. It may be the result of a direct effect of omeprazole on the vascular endothelium[37], as omeprazole also protects human gastric epithelial cells in vitro from indomethacin induced damage[39].

The relationship between omeprazole and prostaglandin on aspirin induced gastric lesion are controversial. Some reports shown that omeprazole increased gastric prostaglandin E_2 formation on gastric mucosa[39,40,41] another contravers[42].

In our present study ranitidine totally abolished on aspirin induced gastric lesions as compared to placebo and to omeprazole. We recently shown H_2 receptor blockers inhibited by 33.4% the gastric mucosal lesions induced by administration[7] of iv aspirin plus. Intragastric HCl, H_2 receptor antagonists are known to protect against such protection is accomplished remains unclear. Studies suggest a protective effect of H_2 receptor antagonist other than by inhibition of acid secretion[10,43,44]. One it is possibility is the inhibition of aspirin-stimulated adenylate cyclase activity in rat gastric mucosa bathed with aspirin[48] or related to cytoprotective effects[10,44,48].

Our study showed a statistically significant advantage of ranitidine to omeprazole in reducing gastric mucosal lesions. A clinical trial 300 mg ranitidine per day, would therefore be justified in patients at risk of gastric damage from aspirin and non-steroidal anti-

inflammatory drugs. Recent prospective studies in patients have shown that ranitidine[50] and misopstrol[51] attenuate the damaging effects of non-steroidal anti-inflammatory drugs on the upper gastrointestinal tract.

This study demonstrates that omeprazole and ranitidine have a statistically significant preventive effect on aspirin induced gastric lesions, when compared to placebo and ranitidine more potent-than omeprazole. This preventive effect of omeprazole and ranitidine may prove to be clinically very important and warrants futher investigation.

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