Preventive Action of Omeprazole and Ranitidine on Stress Ulcer Formation in Rat

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Özet: STRES ÜLSERLERİNİN ÖNLENMESİNDE OMEPRAZOLE VE RANİTİDİNE'İN ROLÜ

Stres ülserlerinin patogenezinde hiperasiditenin rolü olduğu bilinmektedir. Omeprazole ve ranitidine asit sekresyonunu ayrı mekanizmalarla potent bir şekilde inhibe etmektedir. Bu nedenle omeprazol'un stres ülserlerinin önlenmesindeki etkileri plasebo kontrollü bu çalışmada ranitidine ile karşılaştırmalı olarak incelenmiştir. Çalışmaya alınan 30 adet erkek sıçan (150-200gr) 24 saat aç bırakıldı, ancak su içmelerine izin verildi. Hayvanlar herbiri 10 sıçan içeren 3 gruba ayrıldı. Plasebo alan 1. gruba 1ml serum fizyolojik (SF), 2. gruba omeprazole 0.3 mg/kg, 3. gruba ise ranitidine 3mg/kg aynı hacimdeki volüm ile intraperitoneal (ip) olarak enjekte edildi. İlaçların verilmesinden 1 saat sonra tüm sıçanlara 4 saat süre ile hareketsizlik stresi uygulandı. Deney sonunda hayvanlar öldürüldü, laparotomi yapılarak çıkarılan mideleri büyük kurvatur boyunca açıldı. Mukozadaki peteşi sayısı indekslendi. Peteşi indeksi plasebo grubunda 3.75±0.67 iken omeprazole grubunda 0.8±0.22'ye düştü. Ranitidine grubunda ise ülser indeksi 1.00±0.05 idi. Gerek omeprazole ($p<0.001$) ve gerekse ranitidine ($p<0.01$) stres ülser oluşumunu kontrol grubuna göre stres ülser oluşmasını istatistiki olarak anlamlı bir şekilde önledi. Koruyuculuk etkisi bakımından omeprazole ve ranitidine arasında anlamlı bir fark gözlenmedi.

Sonuçlar omeprozole ve ranitidine'in stres ülserlerinin önlenmesinde etkili olduğunu göstermektedir.

Anahtar Kelimeler: Stres ülseri, hareketsizlik stresi, omeprazole, ranitidine, gastrik ülser, sıçan

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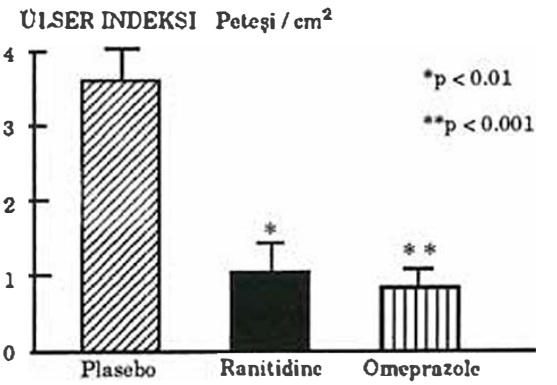
Summary: The relationshipe between omeprazole and stress ulcer on restraint-stress ulcer formation was studied in rats. Thirty male albino rats were used for this experiments. Animals were divided into three groups. Group 1 an intraperitoneal (ip) injection of 0.9 % saline 1 ml, group 2 received an ip injection of omeprazole 0.3 mg/kg, group 3 received an ip injection of ranitidine 3mg/kg. One hour later after treatment, all animals were restrained stress for four hours gastric mucosa were inspecte for lesions, and the ulcer index evaluated. Untreated animal showed multiple lesions of various localisation and size in stomach. In this group the mean lesion index was 3.75±0.67. Intraperitoneal administration of omeprazole reversed 97.9 percent the effect of restraint-stress-induced gastric lesions. In this group lesion index was 0.8±0.22. Administration of ranitidine abolished 73.4 percent gastric lesions. In this group the mean ulcer index was 1.00±0.05. In results both omeprazole ($p<0.001$) and ranitidine ($p<0.01$) significantly prevented stress induced gastric damage.

Key Word: Stress ulcer, restraint- stress, omeprazole, ranitidine, gastric ulcer, rat

Omeprazole, a substituted benzimidazole, is a new long acting, potent, and highly specific inhibitor of gastric acid secretion. Unlike H_2

Table I: Gastric lesion index after 4 hours restraint-stress.

Groups	Index lesion/cm2	Preventive effect(%)
Placebo	3.75±0.67	00.00
Omeprozole*	0.80±0.22	97.90
Ranitidine**	1.00±0.05	73.40
*p<0.001	Compare to placebo	
**p<0.01	Compare to placebo	



Graphic 1. Gastric lesion index after 4 hours restraint-stress.

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 (1). Its antisecretory action has been confirmed (2-4) and the compound has been shown to prevent ulcer formation by a variety of methods, including pylorus ligation and exposure to aspirin solution.

Preliminary data also suggest that omeprazole may have some cytoprotective effect independent of its effect on gastric acid secretion. The drug decreased (51) Cr release from cultured human gastric mucosal cells exposed to sodium taurocholate (5). Other investigators demonstrated that orally administrated omeprazole decreased gastric mucosal injury in rats after exposure to ethanol while intraperitoneal administration was found not to be protective (6).

The basis for using omeprazole for prophylaxis or treatment of stress-related mucosal injury is its powerful inhibition of gastric acid secretion. No clinical trials to date have assessed its efficacy in preventing or treating stress ulceration of the upper gastrointestinal tract and its use fulness in this situation remains hypothetical.

Acid is an essantial prepequisite for the development of gastric stress ulceration (7,8). In the experimental and clinical situation, the minimal luminal hydrogen ion concentration necessary for luminal hydrogen ion concentration necessary for stress ulcers to arise ise a pH of around 4 (9,10). Current management of gastric stress ulceration still occurs (9,11).

Therefore this study has been done to investigate a possible prophylactic effect of omeprazole and ranitidine against stress ulcer formation and to compare this effect to the protection provided with each other.

MATERIAL and METHODS

Thirty male albino rats 150-200 g were used for the experiments. Animals were fasted for 24 h. but allowed access to water ad libitum.

The animals were devided into three groups. Group 1(n: 10) an intraperitoneal (ip) injection of 0.9% saline 1ml, group 2(n: 10) received an ip injection of omeprazole 0.3 mg/kg (Astra), group 3(n: 10) received an ip injection of ranitidine 3 mg/kg. One hour later after treatment, all animals were restrained stress for 4 hours by a standard procedure according to Brodie and Hanson (12). After each experiment, animals were sacrificed by air embolism. Stomachs were quickly removed and opened along the greater curvature. Gastric mucosa was in spected for lesions and the ulcer index evaluated. With the aid of dissecting microscope (X10), we calculated the average length of each lesion in mm and used this figure as the ulcer index (12).

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

RESULTS

After 4 hours of immobilisation all untreated animals showed multiple lesions of various localisation and size in stomach. In this group the mean lesion index was 3.75±0.67. Intraperitoneal administration of omeprazole reversed 97.9 percent the effect of restraint stress induced gastric lesions. In this group the mean ulcer index was 0.8±0.22 ($p<0.001$). Ranitidine abolished 73.4 percent gastric lesions. In this group the mean ulcer index was 1.00±0.05 ($p<0.01$) (Table I, Graphic 1).

DISCUSSION

In our present study shown that omeprazole and ranitidine significantly prevented on restraint-stress-induced gastric lesions.

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 (13) and damages the basal lamina resulting in impaired epithelial restitution (14). In addition, the activity of pepsin is pH dependent and is inhibited at high pH. What ever the mechanism, the observations presented here strongly support the hythesis that gastric acid is crucial in the genesis of stress related gastroduodenal injury.

H_2 receptor antagonists effectively reduce gastric acid output, they often are able to maintain gastric pH above 4 (10).

Omeprazole is recent addition to the expanding group drugs that inhibit gastric acid secretion. It works by a different mechanism of action than other agents in this class, however. Omeprazole inhibits H^++K^+ -adenosine triphosphatase (ATPase), a proton pump that is necessary for extrusion of H^+ from the parietal cells (15), as apposed to the H_2-receptor antagonists, which block the stimulatory action of histamine on gastric parietal cells. Continuous monitoring of intragastric pH reveals that omeprazole is an extremly effective agent for suppressing gastric acid secretion. A single morning dose of 40 mg resulted in a gastric pH of 5.0 or above for 51% of hourly pH determinations over a 24-hour period versus only 3% of measurements made during the control period (16). This elevation in gastric pH produced by omeprazole roughly correspounds to a 1200-fold reduction in gastric acid secretion compared with a 2-fold to 10-fold decrease produced by treatment with conventional doses of currently available H_2-receptor antagonists (16).

Preliminary data also suggest that omeprazole may have some cytoprotective effect independent of its effect on gastric acid secretion. The drug decreased (51) Cr release from cultured human gastric mucosal cells exposed to sodium tauracholate (5). Other investigators demonsrated that orally administrated omeprazole decreased gastric mucosal injury in rats after exposure to ethanol while intraperitoneal administration was found not to be protective. The clinical implications of this study important.

Omeprazole and ranitidine possible to render achlorhydric patients liable to gastric stress ulceration and maintain then in this state as long as are required. Under these conditions it appears that gastric stress ulceration will be prevented. The inffectiviness of other treatments, especially antiacides or anticolinergics, are probably because continuous increasing of gastric pH could not be achieved.

In conclusion, the preventive effect of omeprazole and ranitidine may prove to be clinically very important and warrients futher investigation.

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