Inhibition of Stress Ulcer Formation With Somatostatin Analogue (SMS 201-995) in Rats

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Özet SOMATOSTATİN ANALOĞU (SMS 201-995 ve STRES ÜLSERİ İLİŞKİSİ

Plasebo kontrollü bu çalışmada Somatostatin analoğu'nun (SMS 201-995) stres ülserinin önlenmesindeki etkisi incelenmiştir. Çalışmaya alınan 20 adet erkek sıçan (150-200 gr) 24 saat aç bırakıldı. Ancak su içmelerine izin verildi. Hayvanlar herbiri 10 sıçan içeren 2 grubu ayrıldı. 1. gruba 1ml. serum fizyolojik (SF), 2. gruba SMS-201-995 50 kg. aynı hacimdeki SF ile intraperitoneal olarak yapıldı. Ilaçların verilmesinden 1 saat sonra tüm sıçanlara 4 saat süre ile haraketsizlik stresi uygulandı. Deney sonunda hayvanlar öldürüldü, laparotomi yapılarak çıkarılan mideler büyük kurvatur boyunca açıldı. Lümendeki kan ve mukozadaki peteşi sayısı değerlendirilerek lezyonlar indekslendi. Peteşi indeksi kontrol grubunda 3.75±0.67 iken SMS grubunda 2.87±0.51 ile %23.5 azalma gözlendi. Gruplar arasındaki fark istatistiki bakımdan anlamsızdı. Elde edilen bulgular stres ülserlerinin önlenmesinde SMS'nin anlamlı oranda etkili olmadığını göstermektedir. Bu sonuçlar SMS'nin dozuna bağlı olarak yapılacak yeni çalışmalarla desteklenmesinin gerekli olduğunu düşündürmektedir.

Summary Prophylactic effect of somatostatin analogue (SMS 201-995) on restraint stress ulcer formation was studied in rats. Twenty male albino rats were used for the experiments. Animals were divided into two groups. Group 1 an intraperitoneal (ip) injection of 0.9 % saline 1 ml., group 2 received an ip injection of SMS 201-995 50μ g. One hour later after treatment, all animals were restrainted for 4 hours. Gastric mucosa was inspected 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 SMS 201-995 reversed the effect of restraint stress induced gastric lesions. In this group lesion index was 2.87±0.51. In conclusion SMS 201-995 50mg showed no significant difference from placebo in preventing mucosal damage, was induced by stress ulcer formation in rat. There are many possible reasons why such a results are suprising in view of somatostatin as a cytoprotective drug. Future studies to further evaluate cytoprotection are recommended.

Although there are many problems comparing experimental results in animals with clinical investigations the conclusion may be allowed that SMS 201-995 could open new possibilities in the treatment of ulceration.

Anahtar Kelimeler: Somatostatin analoğu, Stres ülser, Gastrik lezyon

Key Words: Somatostatin analogue, Stres ulcer, Gastric lesion, rat

Somatostatin (SS) exerts an extraordinary range of pharmacologic and physiologic effects which have been summarized in several recent comprehensive reviews (1-3). In animal models it inhibitis secretion of gastric acid pepsin, and gastrin (4-6). In human beings it stimulates gastric mucus production (7), reduces gastric and mesenteric blood flow (8), and inhibits gastric mucosal-cell proliferation (9). Current evidence suggest that SS may effect the pathogenesis of peptic ulcer disease by providing Somatostatin-like immunoreactivity

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(SLI) of gastric antral mucosa has been reported to be lower in people with peptic ulcer disease (10,11). It has also been suggested that normal circulating SS alters the target cells that control acid secretion and gastrin release (13). SS has also been shown to prevent the formation of stress ulceration in rats (14).

The recent availability of a long-acting octapeptide analogue of somatostatin (SMS 201-995) reawakened interest in the role of somatostatin, albeit a modified molecular form, in the prevention of stress ulcer.

It has been suggested that some of these factors are involved in the pathogenesis of stress ulcer production. There fore this study had been done to investigate a possible prophylactic effect of SMS 201-995 on ulcer formation.

MATERIALS AND METHODS

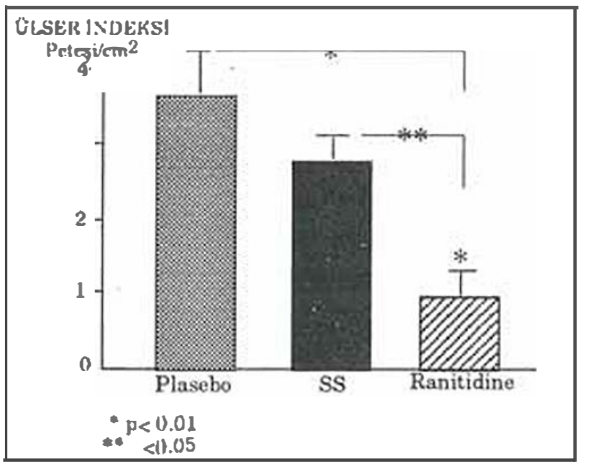
Twenty male albino rats 150-200 g were used for the experiments. Animals were fasted for 24 h, but allowed access to water ad libitum.

The animals were divided into two groups 1 (n:10) and intraperitoneal (ip) injection of 0.9% saline 1 ml, group 2(n:10) received an ip injection of SMS 201-995 (Sandoz Pharmac.) 50 µg.

One hour later after treatment, all animals were restrained for 4 hours by a standard procedure according to Brodie and Hanson (16).

After each experiment, animals were sacrificed by air embolism. Stomachs were quickly removed and opened along the greater curvature. Gastric mucosa was inspected for lesions and the ulcer index evaluated. With the aid of dissecting misroscope (x10), we calculated the average length of each lesion in mm and used this figure as the ulcer index (16).

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



Graphic 1. Ulcer index (mm) in the gastric mucosa for the two groups (mean ± SEM).

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 SMS 201-995 reversed the effect of restraint stress induced gastric lesions. In this group the mean ulcer index was 2.87±0.51, but the preventive effect of SMS 201-995, on stress ulcer production, was not significant difference from control group (Graphic 1).

DISCUSSION

In the present study ip administration of SMS 201-995 50µg reduced gastric damage formation which would otherwise be induced by immobilisation in rats. But, this preventive effect was not satistically significant difference from the placebo.

Although the preventive effect in yet to demonstrated in this study, some investigators showned rate that somatostatin has a potent prophylactic effect on stress ulcer formation in the rat(14).

In animal models SS inhibit secretion of gast-

ric acid, pepsin, and gastrin (4-6). In human beings it stimulates gastric mucus production (7), current evidence suggest that SS may affect the pathogenesis of peptic ulcer disease by providing both cytoprotection and an aggressive acid-pepsin factor (10-12). It has also been suggested that normal circulating SS alters the target cells that control acid secretion and gastrin release (13). These factors are involved in the pathogenesis of stress ulcer production.

The mechanism where by SS inhibits gastric acid secretion is not full understood. It has been demonstrated that SS can potentiate the synthesis and release of endogenous prostaglandin E2 from isolated rat stomach in the presence of carbamylcholine(18). Prostaglandins (PGs) have been shown to behave as cptoprotective agents and potent inhibitors of gastric acid secretion (19,2). In one study, endogenous PGs appeared to be involved in the mechanism by which SS inhibited gastric acid release (21). On the other hand, it has been reported that PGs are not required for the inhibition of gastric acid secretion (22,23). It is conceivable that SS stimulates PGs synthesis and release and that this process may results in the protective effects of SS against stress ulcer formation.

It has shown that if administration of SS inhibits gastric acid secretion and that this inhibition is associated with a significant reduction of gastrin in the gastric juice (24). More over, studies have demonstrated various pharmacological and physiological stimuli which resulted in significant changes in gastric luminal SLI content in man (25). Reaccutly, it reported that infusion of SS inhibited gastric acid secretion and aspirin-induced ulcer formation and increased SLI concentration in gastric juice (26). This findings also suggest that during IV administration of SS, the peptide or an immunoreactive fragment of the peptide may be released into the gastric lumen and may thus function in the lumen to influence gastric acid secretion and ulcer production.

In conclusion, in the present study, SMS 201-995 50 µg showed no significant difference from placebo in preventing mucosal damage, was induced by stress ulcer formation in rat. There are many possible reasons why such a results are suprising in view of the strong positive experimental evidence of SS as a cytoprotective drug (10-12). Future studies to further evaluate cytoprotection are recommended.

Although there are many problems comparing experimental results in animals with clinical investigations the conclusion may be allowed that SMS 201-995 could open new possibilities in the treatment of ulceration.

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