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In vitro effects of famotidine and ranitidine on lower esophageal sphincter tone in rats

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Background/aims: *The aim of this study was to investigate the effects of the H2 receptor antagonists famotidine and ranitidine on lower esophageal sphincter pressure in the rat isolated lower esophageal sphincter preparation contracted with carbachol.* ***Materials and Methods:*** *Lower esophageal sphincter tissues of eight rats for each group were placed in a standard organ bath. After contraction with carbachol, freshly prepared famotidine and ranitidine were added directly to the tissue bath in cumulatively increasing concentrations. Activities were recorded on an online computer using the software BSL PRO v 3.7, which also analyzed the data.* ***Results:*** *Ranitidine caused a small statistically insignificant relaxation in the contracted lower esophageal sphincter at the two applied concentrations. Although $1.5x10^{-5}$ M famotidine did not cause a significant relaxation in lower esophageal sphincter tone, this value for $4.5x10^{-5}$ M famotidine was 9.33%, and the relaxation was significant when compared with controls ($p<0.05$).* ***Conclusions:*** *Neither famotidine nor ranitidine caused any direct significant change in lower esophageal sphincter tone in the therapeutic dose range applied to the organ bath. However, the higher dose of famotidine caused a significant relaxation in the lower esophageal sphincter tone. Further in vivo human studies may affect the usage of these drugs during gastroesophageal reflux disease treatment.*

Key words: Lower esophageal sphincter, famotidine, ranitidine, gastroesophageal reflux disease

Famotidin ve ranitidinin sıçan alt özofagus sfinkter tonusu üzerindeki in vitro etkileri

Amaç: *Bu çalışmanın amacı, H2 reseptör antagonistlerinden famotidin ve ranitidinin, karbakol ile kasılmış alt özofagus sfinkter preparatlarının gerilimi üzerine etkisini araştırmaktır.* ***Gereç ve Yöntem:*** *Her bir grup için 8'er tane sıçandan alınan alt özofagus sfinkter dokuları standart organ banyosuna yerleştirildi. Karbakol ile kasılan alt özofagus sfinkter dokuları üzerine, taze olarak hazırlanmış famotidin ve ranitidin solüsyonları kümülatif olarak artan dozlarda eklendi. Aktiviteler çevrimiçi olarak BSL PRO MP-35 ile kaydedildi ve yine aynı sistem ile datalar analiz edildi.* ***Bulgular:*** *Ranitidinin uygulanan her iki dozunda, kasılmış alt özofagus sfinkter tonusunda istatistiksel olarak anlamsız bir gevşeme meydana geldi. $1.5x10^{-5}$ M famotidin de alt özofagus sfinkter tonusu üzerinde anlamlı miktarda gevşemeye sebep olmamasına rağmen, $4.5x10^{-5}$ M famotidin için bu değer % 9,33'tü ve gevşeme kontrollerle karşılaştırıldığında anlamlıydı ($p<0.05$).* ***Sonuç:*** *Organ banyosuna terapötik dozda uygulanan ne famotidin ne de ranitidin, alt özofagus sfinkter tonusu üzerinde anlamlı bir değişiklik meydana getirmedi. Bununla birlikte, famotidin yüksek doz uygulaması alt özofagus sfinkter tonusu üzerinde anlamlı bir gevşemeye sebep oldu. İlerleyen zamanlarda, in vivo insan deneyleri çalışmaları, gastroözofageal reflü hastalıklarında bu ilaçların kullanımını etkileyebilecektir*

Anahtar kelimeler: Alt özofagus sfinkteri, famotidin, ranitidin, gastroözofageal reflü hastalıkları

INTRODUCTION

Gastroesophageal reflux disease (GERD) is the most common functional esophageal disorder in the world (1). The high-pressure zone at the junction between the esophagus and the stomach is called the lower esophageal sphincter (LES) (2,3). The LES is composed of at least two separate

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muscle layers, circular and oblique (4). The circular smooth muscle of the LES is characterized by spontaneously generated basal tone, and this state creates a pressure barrier at the gastroesophageal junction to prevent reflux of gastric and duodenal contents into the esophagus (5,6). Basal tone of the LES is primarily myogenic in origin but can be modulated by both neural and hormonal factors; nonetheless, the basic mechanisms involved in the control of LES activity are still incompletely understood (2,7). The main pathophysiologic mechanisms proposed to account for GERD are reduced tonic pressures in the LES and transient LES relaxations (TLESRs) (8-10). Gastric acid and duodenal content reflux into the esophagus may play an important role in the pathophysiology of reflux esophagitis. The heartburn and regurgitation that are produced are the characteristic symptoms of GERD (11,12). While gastric pH regulation is the main goal in GERD treatment, inhibition of the TLESRs is another important goal of treatment.

The effective treatment of GERD provides symptom relief and high rates of remission in esophagitis, lowers the incidence of GERD complications, and improves health-related quality of life (13). Histamine, by acting on the H_2 receptors, stimulates gastric acid secretion, which is thought to represent the final mediator of acid secretion; therefore, H_2 receptor antagonists are frequently used for the treatment of acid-related peptic disease and GERD (13-16). Famotidine and ranitidine reduce acid secretion by competitive and reversible blockade of histamine H_2 receptors on the parietal cells of the stomach (13,16). H_2 receptor antagonists inhibit basal acid secretion by approximately 85% (14,15). They are approved by the Food and Drug Administration (FDA) for use in patients with symptomatic GERD (17). The proton pump inhibitors (PPIs) are widely prescribed drugs in the treatment of GERD, but in addition to gastric pH regulation, they also inhibit the contraction of the LES experimentally (18). Although H2 receptor antagonists have been one of the most commonly used treatment choices for GERD, experimental studies about their effects in isolated LES preparations are lacking.

The aim of this study was to investigate the effects of the H2 receptor antagonists famotidine and ranitidine on LES pressure in the rat isolated LES preparation contracted with carbachol and to enlighten clinicians on this very important topic.

MATERIALS AND METHODS

The experimental protocol was approved by the Ethical Committee of Yeditepe University Experimental Medicine Research Institute, and the use of animals was in compliance with the United States National Institutes of Health Guide for the Care and Use of Laboratory Animals. The statistical consultation before the onset of the experiment showed that a minimum of six animals for each study group was enough to assess the statistical significance. Therefore, we had planned to use eight animals for each study group.

Twenty-four rats weighing 250-300 g provided by the Yeditepe University Experimental Research Center (YÜDETAM) were used throughout the study. They were kept in plexiglass cages in a room with controlled temperature and humidity and a 12-hour (h) light/dark cycle and had free access to food and water.

Rats were anesthetized with 10 mg/kg xylazine HCl (Rompun® 2%, Bayer HealthCare AG, Leverkusen, Germany) and 100 mg/kg ketamine HCl (Ketasol® 10%, Richter Pharma AG, Weis, Austria) before decapitation.

A midline incision was performed to open the abdominal cavity, and the LES was carefully dissected out and placed in a petri dish containing Krebs solution at room temperature. Thereafter, the mucosal lining was removed and the sphincteric muscle was set up, as a ring segment 2 mm in width, in Krebs solution contained in a standard 30-ml organ bath. The modified Krebs solution was of the following composition: NaCl, 118.07; KCl, 4.69; $CaCl_2$, 2.52; $MgSO_4$, 1.16; KH2PO4, 1.2; $NaHCO_3$, 25; and glucose, 11.10 mmol/L. Krebs solution was continuously aired with 95% oxygen - 5% carbon dioxide gas mixture and kept at 37±0.5 °C throughout the experimental period. The tissues were tied to stainless steel hooks at one end of the organ bath; the other end was connected to a force transducer (FDT 05, May, COMMAT Iletisim Co, Ankara, Turkey) under a resting tension of around 1 g. LES ring activities were recorded on an online computer via a four-channel transducer data acquisition system (MP35, BIOPAC Systems Inc.; Goleta, CA, USA) using the software BSL PRO v 3.7 (BIOPAC Systems Inc.; Goleta, CA, USA), which also analyzed the data.

The following compounds were used: carbachol chloride (carbamylcholine chloride, Sigma – Aldrich Chemical Co.; St. Louis, MO, USA), famotidi-

ne (UCB Pharma A.Ş., İstanbul, Turkey) and ranitidine (GlaxoSmithKline İlaçları A.Ş., İstanbul, Turkey). Solutions were prepared daily in distilled water and kept at + 4 °C during the experiments. Following a 60 minute (min) equilibration period for stabilization, contractile response to carbachol was obtained by application of single dose of carbachol to have a final concentration of 10^{-6} M in the organ bath. After the contractions reached a plateau, concentration-response relationships for famotidine (final organ bath concentrations $1.5x10^{-6}$ M, $1.5x10^{-5}$ M and $4.5x10^{-5}$ M, with 15 min allotted between each dose) and ranitidine (final organ bath concentrations 10^{-5} M, 10^{-4} M and $3x10^{-4}$ M, with 15 min allotted between each dose) were obtained in a cumulative manner. Control experiments were also run with only distilled water added to the organ bath. At the end of each experiment, tissues were weighed and the pH of the final Krebs solution was measured.

Statistical Analysis

For statistical evaluation, analysis of variance (one-way ANOVA) was performed with the Statistical Package for the Social Sciences (SPSS) program for Windows version 18 (SPSS Inc.; Chicago, IL, USA). Values of $p<0.05$ were considered as statistically significant.

RESULTS

There were no significant differences in LES strip wet weights used for the study. In our study, $4.5x10^{-5}$ M concentration of famotidine caused a significant relaxation in the carbachol-contracted LES preparations, while no such effect was observed with any other concentration of famotidine or any concentration of ranitidine. The relaxations were quantified by integrating area under the curve for each concentration. Mean integral values and percent relaxations of eight preparations were compared for statistical evaluation.

Figure 1 shows that ranitidine caused a slight decrease in LES tone compared to the control group, but this response did not reach significance. On the other hand, as can be observed in Figure 2, application of famotidine in a cumulative manner resulted in significant relaxations of LES preparations at $4.5x10^{-5}$ M concentration.

In the carbachol-contracted LES preparations, $1.5x10^{-6}$ M and $1.5x10^{-5}$ M famotidine caused 1.95% and 5.91% relaxations, respectively, which were not significant. However, mean integral relaxation value for $4.5x10^{-5}$ M was 9.33%, and this relaxation was significant when compared with controls ($p<0.05$).

DISCUSSION

The primary aim of the present work was to assess the *in vitro* effects of famotidine and ranitidine on LES tone in rats. To our knowledge, this is the first time the in vitro effects of famotidine and ranitidine on LES tone were assessed.

The major finding of our study was that $4.5x10^{-5}$ M famotidine caused a significant relaxation in the LES tone. Although $1.5x10^{-5}$ M famotidine caused a 5.91% relaxation, it did not reach a statistically significant level. Ranitidine did not cause such effects in any concentration tested. This finding may be explained by the difference in potential effects of these two agents. Equally potent doses of these

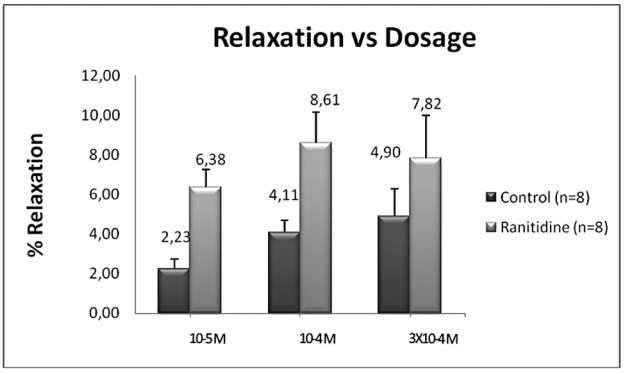

Figure 1. Ranitidine did not induce a significant relaxation on lower esophageal sphincter (LES) preparations *in vitro*. Each bar represents percent relaxation ± SEM for both control and experiment groups. Numbers in parentheses indicate the number of preparations used from different animals.

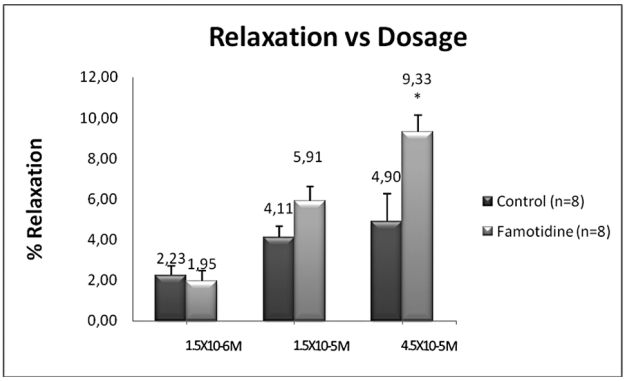

Figure 2. $4.5x10^{-5}$ M famotidine induced significant relaxation on lower esophageal sphincter (LES) preparations *in vitro* (* $p<0.05$). Each bar represents percent relaxation ± SEM for both control and experiment groups. Numbers in parentheses indicate the number of preparations used from different animals.

drugs had similar onset of action, but the duration of action of famotidine was reported as being 30% longer than the duration of action of ranitidine. Further, it is known that famotidine is 7.5–9 times more potent than ranitidine (19,20). As these reports had discussed the potential efficacy of famotidine and ranitidine on gastric acid secretion, we suggest that famotidine may have a similar more potent action on LES function by an unknown mechanism.

GERD occurs when gastric contents reflux into the esophagus in excess of normal limits (21). A valve mechanism exists between the esophagus and the stomach, formed by the LES, the diaphragm, the His angle and the phrenoesophageal membrane. The junction between the stomach and the esophagus is a specialized region comprising the LES, and this structure prevents reflux of gastric contents back into the esophagus. Decreased LES tone may occur in GERD, and despite a normal LES pressure, GERD can develop due to TLESRs. When TLESRs become more frequent and prolonged, it can contribute to reflux disease (21-23). Heartburn and acid regurgitation are the most common symptoms of GERD, and GERD can result in esophageal mucosal injury and erosive esophagitis (24). GERD symptoms are troublesome and have a substantial negative impact on a patient's quality of life (25). Green et al. (26) reported a significant and strong association between total acid contact time and GERD symptoms. The Montreal consensus conference defined GERD as "a condition which develops when the reflux of gastric contents causes troublesome symptoms and/or complications". When this condition persists, damage to the esophagus by gastric hydrochloric acid and other noxious agents, including pepsin, was seen (27). Nonerosive reflux disease (NERD) is a subcategory of GERD in which patients show no erosive esophagitis on upper endoscopy, and it accounts for 60-70% of GERD (28-30).

Inhibition of gastric acid secretion has become the traditional medical treatment for reflux esophagitis in GERD. One of the commonly used medical agents has been H_2 receptor antagonists; however, PPI_s have recently become superior to H_2 receptor antagonists in treating esophageal mucosal injury and erosive esophagitis due to GERD (31-34). Despite an adequate treatment regimen, the patient population who are poor or non-responders to PPI treatment will constitute 10–30% of all GERD patients. Treatment with acid suppression only changes the pH of the refluxate without stopping reflux through a functionally or mechanically incompetent LES (35,36). Other non-acid components present in the reflux material may contribute to the refractory nature of symptoms and esophagitis. PPI failure is the most common presentation of refractory GERD in gastrointestinal practice. Delayed gastric emptying, patient comorbidities such as diabetes mellitus, nighttime reflux and alkaline duodenogastroesophageal reflux, and PPI resistance are some of the underlying mechanisms for PPI failure (37). In some patients, even the highest approved dose of PPI fails to sufficiently suppress gastric acid secretion due to polymorphisms in the genes encoding CYP2C19, which metabolizes PPIs. Patients with CYP2C19 polymorphisms do not benefit from the therapeutic effects of PPIs even at very high doses (38). As TLESRs contribute to the mechanism responsible for GERD, inhibition of the rate of TLESRs will be one of the main goals of GERD treatment in addition to gastric pH regulation (36,39). In this study, we aimed to investigate the negative or positive impact of commonly used H_2 blockers on LES relaxation. H_2 blockers such as famotidine, nizatidine and roxatidine are excreted in the urine with little involvement in hepatic metabolism and are not affected by the polymorphisms present in hepatic enzymes. Drug interactions are also not common among them (40). Furthermore, H_2 blockers inhibit nocturnal acid secretion that depends largely on histamine as well (41). There are different therapeutic strategies for refractory GERD, such as changing the usage of PPIs to twice a day, adding bedtime H_2 blockers to the PPI regimen or using high doses of PPI or H_2 blockers. No difference in gastric acid suppression between PPI twice daily and PPI twice daily plus H_2 blockers at bedtime was reported after one week of therapy (42). However, researchers did not conduct experiments regarding the effects of H_2 receptor antagonists on the isolated LES. In our study, we showed that famotidine relaxes the LES at high dose levels with an unknown mechanism. This finding suggests that usage of high-dose regimens as an alternative option for symptomatic control of refractory GERD may result in worse management of these patients.

In our study, neither famotidine nor ranitidine caused any direct significant change in LES tone in the normal (therapeutic) dose range applied to the organ bath. However, famotidine at the high dose caused a significant relaxation in the LES to-

ne. Considering the nocturnal acid suppressant effects of ranitidine and famotidine, their lack of drug interactions and their not being affected by CYP2C19 polymorphisms, the use of H_2 blockers may be recommended widespread in the treatment of GERD in combination with other drugs such as prokinetics, neurotransmitter antagonists or anticholinergics, at such time when these results have been verified by in vivo experiments and studies conducted in humans.

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